

**THE
EPIDEMIOLOGY AND AETIOLOGY OF
A RISING INCIDENCE OF
PAPILLARY THYROID CARCINOMA
IN TASMANIA**

by

John Richard Burgess MD, FRACP

Discipline of Medicine

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STATEMENT OF AUTHENTICITY

This thesis contains no material that has been accepted for the award of any other higher degree or graduate diploma in any tertiary institution.

I am responsible for initiating and undertaking the work described in this thesis. The full extent to which others have contributed to the data contained herein is detailed in the Acknowledgements and Bibliography.

John Richard Burgess

A handwritten signature in black ink, consisting of a stylized 'J' followed by a horizontal line and a small flourish.

Date 21 / 06 / 2007

AUTHORITY OF ACCESS

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Date 21 / 06 / 2007

DEDICATION

This thesis is dedicated to my family -- to my Jennifer; for support and encouragement --
to James, William and Matthew; may they too find enjoyment in learning.

PREFACE

When I commenced clinical practice as an endocrinologist in Tasmania during the mid-1990s, I was intrigued by reports from a number of jurisdictions of an increasing incidence of papillary thyroid carcinoma (PTC). Varying causes had been proposed. Spurious methodological factors such as improving case registration by Cancer Registries, changes in the morphological classification of thyroid tumours and finer sectioning of thyroidectomy samples were postulated. Similarly, a true change in PTC incidence due to increased exposure to risk factors such as ionising radiation and changes in iodine nutrition were also proposed as explanatory.

Tasmania is an island State of the Australian Commonwealth with a stable population structure, sophisticated medical infrastructure and a well characterised history of iodine deficiency. This presented the opportunity for using the Tasmanian population as a model to evaluate the cause of observed PTC incidence trends.

The research presented in this thesis was undertaken by myself between 1995 and 2006 in an attempt to answer fundamental questions regarding incidence trends for PTC - namely, has there been a true increase in the incidence of PTC and if so, what factors underlie this change? My role encompassed conceptual planning, the development and submission of applications for funding, preparation of documents for Institutional Ethics Committee approval, patient recruitment, database construction, statistical analysis, and preparation of manuscripts for publication. Candidature for this PhD was approved and undertaken in keeping with the provisions of Appendices A.4 and A.5 – previously published research.

PUBLICATIONS FROM THIS THESIS

This thesis contains six chapters of original research that are either published (five) or in preparation for publication (one).

Chapter 2

Burgess JR. Temporal trends for thyroid carcinoma in Australia: a rising incidence of papillary thyroid carcinoma (1982 – 1997). *Thyroid*. 2002;12:141-149.

Chapter 3

Burgess JR, Dwyer T, McArdle K, Tucker P. The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978-1988) during a transition from iodine sufficiency to iodine deficiency. *J Clin Endocrinol Metab* 2000;85:1513-1517.

Chapter 4

Burgess JR, Tucker P. 2006 Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine needle aspirate cytology. *Thyroid*. 2006;16:47-53.

Chapter 6

Burgess JR, Skabo S, McArdle K, Tucker P. Temporal trends and clinical correlates for the ret/PTC mutation in papillary thyroid carcinoma. *ANZ J Surg*. 2003;87:31-35.

Chapter 7

Burgess JR, Wilkinson R, Ware R, Greenaway TM, Percival J, Hoffman L. Two families with an autosomal dominant inheritance pattern for papillary carcinoma of the thyroid. *J Clin Endocrinol Metab* 1997;82:345-348.

RELATED PUBLICATIONS DURING CANDIDATURE

McKay JD, Lesueur F, Jonard L, Pastore A, Williamson J, Hoffman L, **Burgess JR**, et al. Localisation of a susceptibility gene for familial non-medullary thyroid carcinoma to chromosome 2q21. *Am J Hum Genet.* 2001;69:440-446.

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Guttikonda K, **Burgess J**, Hynes K, Boyages S, Byth K, Parameswaran V. Recurrent iodine deficiency in Tasmania, Australia – A salutary lesson in sustainable iodine prophylaxis and its monitoring. *J Clin Endocrinol Metab.* 2002;87:2809-2815

Hynes KL, Blizzard CL, Venn AJ, Dwyer T, **Burgess JR**. Persistent iodine deficiency in a cohort of Tasmanian school children: associations with socio-economic status, geographical location and dietary factors. *Aust N Z J Public Health.* 2004;28:476-481.

Seal JA, Doyle Z, **Burgess JR**, Taylor R, Cameron AR. Iodine status of Tasmanians following voluntary fortification of bread with iodine. *Med J Aust.* 2007;186:69-71.

Burgess JR, Seal JA, Stilwell GM, Reynolds PR, Taylor RE, Parameswaran V. A case for universal salt iodisation to correct iodine deficiency in pregnancy: another salutary lesson from Tasmania. *Med J Aust.* 2007;186:574-576.

ABBREVIATIONS

Age standardised incidence rates (ASR)

Anaplastic thyroid carcinoma (ATC)

Computed tomographic (CT)

Deoxyribonucleic acid (DNA)

Follicular thyroid carcinoma, (FTC)

Fine needle aspiration biopsy (FNAB)

Follicular variant of PTC (fv-PTC)

Iodine deficiency (ID)

Magnetic resonance (MR)

Medullary thyroid carcinoma (MTC)

New South Wales (NSW)

Not otherwise specified (NOS)

Papillary thyroid carcinoma (PTC)

Queensland (QLD)

Reverse transcription-polymerase chain reaction (RT-PCR)

Ribonucleic acid (RNA)

South Australia (SA)

Standard Error of Mean (SEM)

Thyroid carcinoma (TC)

Thyroglobulin (TG)

Thyroid Stimulating Hormone (TSH)

Western Australia (WA)

ACKNOWLEDGEMENTS

This thesis contains work undertaken by myself in conjunction with a number of collaborators and co-authors who contributed various elements of technical, laboratory and clinical expertise. Without the assistance of these this thesis would not have been possible. The role of co-contributors is acknowledged both in the authorship of published work and as detailed below.

I am grateful for the support provided by Dr Linda Hoffman, whose initial clinical observations regarding familial PTC in Tasmania provided the basis for subsequent research and publication in this area. I am similarly indebted to my supervisor Professor David Kilpatrick for the support and flexible learning environment provided during preparation of this thesis. I am thankful for the general advice, assistance and encouragement provided by my colleagues Drs Greenaway and Parameswarran during the course of my research.

Dr Paul Tucker, an histopathologist and colleague, provided invaluable expertise in review and reclassification of thyroid carcinoma archival samples, as well as facilitating links between data resources in the public and private sectors. I am appreciative of guidance and assistance from Dr Stewart Skarbo, Dr Venkat Parameswaran and Ms Lyn Blackwell in helping me develop the laboratory skills required for performing molecular studies for the *RET/PTC1* rearrangement described in Chapter 6. I gratefully acknowledged the advice provided by Dr D Learoyd and Professor B Robinson, Royal North Shore Hospital, New South Wales, Australia; as well as their assistance in making available the TPC-1 cell line (originally from Dr S. M. Jhiang, Columbus, OH, USA).

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The collation of the statewide data set for thyroid procedures would not have been possible without the generous support of numerous individuals and organisations. In particular, Hobart Pathology, Launceston Pathology and the various Tasmanian public and private hospitals, all of whom provided assistance and advice. I also thank the many general practitioners and medical specialists who responded to requests for information. The assistance others provided in relation to the research presented in this thesis is also gratefully recognised in the authorship and specific acknowledgements associated with the published research presented in the Appendix. Finally, I wish to thank the many thousands of Tasmanians; thyroid cancer patients and members of the general public who responded to questionnaires that contributed to the research presented in this thesis.

My research has been supported by research grants from the Tasmanian State Government (Dick Butterfield Fellowship), the Royal Hobart Hospital Research Foundation and the Cancer Council of Tasmania.

STATEMENT OF THE PROBLEM

Papillary thyroid carcinoma (PTC) is the most frequently diagnosed endocrine malignancy. Cancer registries in many countries have identified a substantial increase in the reported incidence of PTC over the past half-century. The explanation for this remains to be elucidated.

Improved PTC case ascertainment by cancer registries, heightened histopathological recognition of small and subclinically PTC, increased use of neck ultrasonography and greater recourse to fine needle aspiration biopsy in evaluation of thyroid nodules may be contributory. An increase in the underlying occurrence of PTC is also possible, with exposure in childhood to ionizing radiation as well as changing levels of iodine nutrition potential underlying factors.

In this thesis I sought to answer the following questions:

- 1 Has the incidence of PTC increased in Australia?
- 2 Is there evidence of geographic variation in PTC incidence within Australia?
- 3 Is the Tasmanian population a suitable model for evaluating the basis for Australian PTC incidence trends?
- 4 Are changes in observed PTC incidence due to changes in histopathological diagnostic criteria or Cancer Registry case ascertainment?
- 5 What is the contribution of increased diagnosis of microscopic and clinically “occult” PTC to observed incidence trends?

- 6 Are geographic patterns of PTC incidence related to the historical or contemporary distribution of iodine deficiency in Australia?
- 7 Does iodine nutrition influence the PTC incidence by either altering tumour pathogenesis or by indirectly increasing the likelihood of diagnosing “occult” PTC?
- 8 Is there evidence for past exposure to ionising radiation as an aetiological driver for contemporary PTC incidence?
- 9 Is there evidence for heritable susceptibility to PTC influencing observed incidence trends?
- 10 Is it possible to estimate the relative contributions of ascertainment bias and changes to the underlying biological incidence in producing contemporary PTC incidence trends?

AIMS

1. To assess temporal trends for thyroid carcinoma in Australia and determine if PTC incidence has increased.
2. To determine the validity of the Tasmanian population as a model for understanding PTC incidence trends both in Australia and internationally.
3. To determine the contribution of non-biological factors (changes in morphological classification, Cancer Registry ascertainment and alterations in clinical practice paradigms) in shaping PTC incidence trends.
4. To determine the contribution of both established and putative PTC risk factors (ionising radiation, genetic susceptibility and iodine nutrition) in shaping PTC incidence trends.

HYPOTHESIS

1. The Tasmanian community provides a population model for investigating national incidence trends for PTC.
2. Non-biological factors (bias due to alterations in medical practice and data management systems) account for the majority of the apparent rise in PTC incidence observed over recent decades.
3. A true increase in underlying PTC incidence accounts for a small, but important component of observed PTC incidence trends.

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ABSTRACT

Thyroid carcinoma (TC) is the most prevalent endocrine malignancy. Four main subtypes are recognised - papillary thyroid carcinoma (PTC), follicular thyroid carcinoma, medullary thyroid carcinoma and anaplastic thyroid carcinoma. PTC accounts the majority of diagnoses. As is typical of most thyroid disorders, women are affected approximately four times more frequently than men. The absolute incidence of PTC varies significantly between geographic locations and racial groups, suggesting an important interaction between environmental and genetic risk factors.

Aside from relative differences in absolute PTC incidence between different communities, a significant increase in PTC incidence has also been observed within many populations over recent decades. In some jurisdictions the incidence of PTC has increased more than two fold. Industrialised as well as developing nations have been affected. Possible explanations include artifact due to changes in both medical practice and tumour registration by Cancer Registries. However, a true biological change in PTC pathogenesis and incidence is also possible. Family history and exposure to ionizing radiation are the most clearly established risk factors. Iodine nutrition may also influence the risk of thyroid malignancy, both by modulating thyroidal radioiodine uptake as well as by directly influencing the pathogenesis of benign and malignant thyroid disease.

My research reviewed Australian national TC incidence trends during the 1980's and 1990's, identifying a rise of between 4.0% and 24.7% per annum in the incidence of PTC across the Australian states. This rise was most obvious in the eastern seaboard states, mapping to those states with the lowest historical levels of iodine nutrition. The greatest rise in PTC incidence was observed in Tasmania, an island State of the Australian Commonwealth, where PTC incidence increased by 24.7% per annum. Tasmania has a well-characterised history of iodine deficiency and a stable demographic structure with a centralised health care system and established Cancer Registry. These characteristics provided an opportunity for evaluating in detail the basis for the more widely observed rise in PTC incidence.

A detailed evaluation of Tasmanian Cancer Registry data over the 21-year period 1978-'98, confirmed that the incidence of PTC had increased by 450% in females and 210% in males. Furthermore, validation of Cancer Registry case ascertainment by *de novo* reconstruction of a Tasmanian TC data-set (using source pathology and hospital documentation), confirmed 93.9% completeness for existing PTC case ascertainment by the Cancer Registry over the study period. Similarly, a review of histopathological diagnoses did not demonstrate any significant change in the morphological classification of TC during this time. These findings exclude changes in either case reporting or tumour classification as the primary cause for observed PTC incidence trends.

The key trend underlying observed changes in PTC incidence was an increase in diagnosis of small ($\leq 1\text{cm}$) PTC that were asymptomatic at the time of resection.

Further studies evaluated the prevalence of both clinical and subclinical (by ultrasonography) nodular thyroid disease in the Tasmanian population. Thyroid ultrasonography revealed nodules in 43.4% of individuals evaluated, the majority (88%) of whom had no previously *recognised* history of thyroid disease. Non-specific neck imaging therefore had the potential to identify clinically inapparent thyroid nodules.

Contemporary evaluation protocols for asymptomatic and incidentally discovered thyroid nodules promote the use of fine needle aspiration biopsy (FNAB) and specimen cytology. An assessment of trends for utilization of thyroid FNAB identified an increase of 17.6% per annum and 66.2% per annum for males and females respectively during the period 1988- 98. As the prevalence of clinically silent PTC ≤ 1 cm diameter ("occult" PTC) is reported to be approximately 5% in thyroid nodules, contemporary patterns of neck imaging and the subsequent FNAB evaluation of subclinical thyroid nodules might explain much of the recently observed rise in incidence of PTC.

I further evaluated the relationship between iodine nutrition and PTC incidence. Comparison of documented changes in iodine nutrition in Tasmania during the past five decades against observed PTC incidence trends showed the increase in PTC incidence occurred during a period when the Tasmanian population was undergoing transition from iodine sufficiency to mild iodine deficiency (after the almost 30 years of optimal iodine nutrition that followed correction of endemic iodine deficiency in the mid-1960's). This observation was unexpected given much of the existing epidemiological evidence links poor iodine nutrition to a reduced proportion of PTC relative to other thyroid malignancies, and a lower incidence of PTC compared to iodine replete populations.

A study was undertaken to evaluate the impact of Tasmania (historically the most iodine deficient Australian state and the region with the greatest contemporary rise in PTC incidence) as a place of birth and residence, on the likelihood of developing benign and malignant thyroid disease. There was a significant association for goitre and thyroidectomy with childhood lived in Tasmania. The association was non-significant for the development of TC. Therefore, increased PTC incidence in Tasmania is potentially explicable on the basis of greater diagnosis of “occult” PTC, most probably diagnosed at the time of investigation and management of benign iodine deficiency related thyroid disease.

I also identified evidence to suggest an increase in the underlying incidence of clinically relevant PTC. Analysis of Tasmanian cancer registry data confirmed a 260% increase in large (>2.0cm) PTC between 1978 and 1998. Moreover, it was notable that despite the rise in incidence of PTC versus FTC, changes in two-, five- and ten- year mortality rates for PTC remained parallel to those of FTC during the study period. As “occult” PTC usually exhibit a benign natural history, an increase in PTC incidence solely due to greater recognition of “occult” PTC would be expected to produce a disproportionate improvement in survival for patients with PTC relative to FTC.

Ionizing irradiation of thyroid tissue in childhood is the best characterized aetiologic factor for thyroid neoplasia. Both benign and malignant tumours are predisposed, with PTC the most frequent malignant sequela. Studies suggest PTC arising after long latency following thyroid irradiation may exhibit a mutation (the *RET/PTC1* rearrangement) with

a prevalence higher than for PTC from non-irradiated populations. In the absence of objective radiation exposure data, I attempted to use the *RET/PTC1* mutation as surrogate marker for past exposure to ionizing radiation. Tasmanian PTC diagnosed between 1978 and 1998 were studied to determine the temporal trends for prevalence of *RET/PTC1*. However, a clear relationship between PTC incidence trends and *RET/PTC1* prevalence was not found. Despite this, it was notable that the absolute prevalence of the *RET/PTC1* rearrangement in Tasmanian PTC was greater than expected and was consistent with the prevalence in irradiated populations. Moreover, a significant clinicopathological association for the *RET/PTC1* rearrangement was identified. Tumours positive for the *RET/PTC1* rearrangement were of larger size and more likely to exhibit lymph node metastases than those without the mutation.

The role of heritable susceptibility to PTC and the potential for a founder effect influencing Tasmanian PTC incidence trends was also assessed. A family history of TC was described by 14.1% of Tasmanian patients diagnosed with PTC. Two large PTC kindreds demonstrating an autosomal dominant inheritance pattern for PTC accounted for the majority of familial cases. However, the absolute contribution of autosomal dominant PTC to overall statewide incidence trends was small. A founder effect did not explain PTC incidence patterns in Tasmania.

The research I have undertaken provides a useful insight into the genesis of Australian national PTC incidence trends. Whilst there is evidence to support a small increase in the underlying incidence of clinically relevant PTC, the main cause for the observed rise in PTC incidence can be attributed to increased ascertainment of “occult” papillary

microcarcinoma. The findings of my research highlight the potential adverse health consequences of inappropriate neck imaging and reinforce the importance of appropriate education for medical practitioners regarding the rational use of thyroid ultrasonography.

CHAPTER 1

Background Literature

THYROID ANATOMY AND PHYSIOLOGY

Anatomy and Embryology

The thyroid gland comprises two lobes and an isthmus. Each lobe is approximately 4cm in length, 2cm in width and 2cm in thickness with a vascular supply derived from the superior thyroid artery and the inferior thyroid artery(1, 2). On microscopy, the thyroid is composed of follicles fed by an extensive capillary network. Each follicle comprises a single sheet of follicular cells (thyrocytes) surrounding a colloid filled lumen. Follicles are arranged in bundles separated by septae of connective tissue. Contained within the connective tissue surrounding the thyroid follicles are the parafollicular C cells that produce calcitonin(1-3).

The thyroid is first evident embryologically at approximately one month post conception as a thickening of the pharyngeal epithelium, subsequently forming a diverticulum from the pharyngeal floor that fuses with the ventral aspect of the fourth pharyngeal pouch (1-3). Thyroglobulin (TG) begins to be synthesized during the second month of gestation and the ability to concentrate iodine is evident by the end of the first trimester. The fetal pituitary synthesizes thyroid stimulating hormone (TSH) early in the second trimester and thereafter both maternal and fetal thyroid hormones contribute to fetal hormone requirements (2-5).

Thyroid Hormone Synthesis

Iodine is an essential substrate for thyroid hormone synthesis(2, 6, 7). Inorganic iodide is concentrated by the thyroid via an energy dependent sodium iodide symporter(8-10).

Iodine is organically bound to thyroglobulin by a reaction involving thyroid peroxidase, which catalyses the iodination of tyrosyl residues of thyroglobulin to produce iodotyrosines(7). The iodotyrosines are subsequently coupled to produce the active iodothyronines, tetra-iodothyronine (T_4) and tri-iodothyronine (T_3). T_4 and T_3 remain bound within the thyroglobulin by peptide linkages until cleaved from thyroglobulin by proteolysis (2).

TSH receptor activation drives thyroid hormone synthesis at various levels including active transport of iodine into the thyrocyte, synthesis of thyroglobulin, proteolysis of colloid and release of active thyroid hormones into circulation(1, 2, 7, 8). The secretion of TSH is mediated by hypothalamic release of thyrotropin releasing hormone (TRH), that in turn is regulated by central receptors located in both the hypothalamus and pituitary, which are sensitive to circulating thyroid hormone levels(1, 11, 12). TSH also provides trophic stimulus for growth and replication of the thyroid follicular cells.

Iodine Nutrition

A minimum of 100mcg of elemental iodine is required per day to prevent the development of iodine deficiency (13, 14). Both inorganic and organically bound iodine are ultimately absorbed from the gastrointestinal tract and small quantities are lost in through the skin and stool. Most iodine, however, is rapidly taken up by the thyroid or cleared via the kidneys(2, 10, 15). Renal iodine clearance is determined by glomerular filtration rate, uninfluenced by active processes (1, 15).

There is marked variation in dietary iodine intake both within and between human populations (16-18). Whist dietary customs such as the routine consumption of seaweed

and other iodine rich foodstuffs are important, in most circumstances iodine intake is predominantly determined by the underlying geology of a community's geographic location. Up to one third of the world's population live in regions that contain borderline deficient levels of soil and water iodine(16, 18, 19). The water and foods derived from geologically deficient regions consequently contain insufficient levels of iodine to sustain normal thyroid function (2, 14, 16, 20).

A diet deficient in iodine produces a variable spectrum of disease, influenced by both the degree of iodine deficiency as well as secondary genetic and environmental factors(21-23). The broad spectrum of derangement resulting from iodine deficiency has led to the use of the term Iodine Deficiency Disorders (IDD) (2, 6, 13, 24-26). Whilst goitre is the most characteristic and physically evident abnormality associated with iodine deficiency, other consequences include variable degrees of intellectual and neurological impairment, altered reproductive function and modulation of risk for autoimmune thyroid disease and thyroid neoplasia (2, 6, 13, 24-34).

THYROID DISEASE

General

The spectrum of thyroid disease includes both structural and functional thyroid anomalies(35-37). The most frequently encountered derangements are diffuse thyroid enlargement, nodular thyroid disease, hyperthyroidism, hypothyroidism and thyroid malignancy. The aetiology of thyroid disease typically stems from abnormal iodine nutrition, autoimmune disease and neoplasia(1, 2).

Hypothyroidism

Hypothyroidism can arise as either primary thyroid dysfunction or as a secondary abnormality involving the hypothalamus or pituitary(36). Primary hypothyroidism due to autoimmune disease accounts for the vast majority of cases. Autoimmune (Hashimoto's) thyroiditis is a chronic autoimmune condition associated with raised levels of anti-thyroid peroxidase(2, 36). The overall community prevalence is approximately 2%, and like many thyroid disorders, women are more frequently affected than males (38, 39). Thyroid hypofunction is manifest as a spectrum from mildly raised TSH in the presence of a normal free thyroxine through to clinically overt hypothyroidism with an elevated TSH concentration and reduced peripheral thyroid hormone levels(40). The most reliable predictive factors for determining those individuals who will progress to overt hypothyroidism is the thyroid peroxidase antibody status and the level of TSH(35, 41). Patients frequently present with insidious onset of lethargy, weight gain and a range of other non-specific symptoms. Replacement of thyroid hormone with synthetic thyroxine is the standard therapy for this condition(1, 2, 42-44).

Hyperthyroidism

As is the case for hypothyroidism, hyperthyroidism is a pathologically heterogeneous entity unified by the primary abnormality of excessive thyroid hormone levels(37). The population prevalence varies with iodine intake, but is in the order of 0.5-2 % and as with other thyroid disorders, women are approximately 5 fold more frequently affected than males(37, 39). In young and middle-aged women autoimmune thyroid disease (Graves' disease) due to a stimulatory autoantibody capable of activating the TSH receptor is the

most common cause(37). In older individuals, particularly those residing in iodine deficient areas, autonomously functioning (toxic) thyroid nodules are frequently the cause (24, 45, 46). Rarely, excessive stimulation of the thyroid by inappropriate TSH hypersecretion, ectopic thyroid tissue (such as struma ovarii) and acute thyroid inflammation are the cause of hyperthyroidism(37).

Iodine Deficiency and Benign Thyroid Disease

The clinical presentation of thyroid dysfunction is modulated by the iodine nutritional status of the population studied(24, 47, 48). Laurberg *et al* have shown that in comparison with the relatively iodine sufficient population of Iceland, a mild to moderately iodine deficient population in Jutland demonstrated a later onset of Graves' disease, a lower rate of autoimmune hypothyroidism and a high frequency of hyperthyroidism in older individuals due to autonomous (toxic) multinodular goitre(25, 48). Iodine nutrition therefore appears to influence not only the evolution of structural thyroid disease, but also the development and expression of autoimmune thyroid disease(22, 23, 47).

The evolution of thyroid disease in the setting of iodine deficiency is a gradual process determined not only by the severity of iodine deficiency, but also by a range of constitutional factors such as genetic susceptibility(21, 46). Early in the pathogenesis of iodine deficient goitre, thyrocyte hypertrophy and hyperplasia occurs even within the context of TSH and FT₄ levels which typically remain within bounds of the reference range(21, 46). Over time, non-toxic, diffuse goitre develop nodular elements. In the early stages of nodular evolution, hyperplastic expansion occurs, and in some areas thyroid

nodularity supervenes due to both polyclonal and monoclonal expansion by sequential acquisition of somatic mutations (46). Micro-heterogeneity of thyrocyte structure and function can progress by way of these acquired mutations of genes encoding growth and functional regulatory proteins, such as those for the TSH receptor and Gs α subunit stimulation of adenylyl cyclase(46, 49). Ultimately, such nodules acquire functional autonomy, the majority (60-70%) of which are monoclonal in origin (21, 46).

A goitre may be defined as an abnormal enlargement of the thyroid gland(1, 2, 50). Whilst the exact volumetric criteria for defining goitre varies between authors, volumes greater than 13 -18ml in adult females and 18 -25ml in males have been proposed, with an age or body surface area criteria for defining goitre in children(2, 51, 52). Whilst early studies of goiter prevalence used clinical evidence of thyroid enlargement (either visible or palpable thyromegaly), contemporary methods using ultrasonographic assessment allow identification of lesser degrees of subclinical thyromegaly(24, 50, 53). Ultrasounographic assessment is now central to the definition of goitre, which despite important operator-dependent variability, permits detailed assessment of internal thyroid architecture and measurement of overall thyroid dimensions for calculation of thyroid volume(51, 53).

Simple goitre (non-toxic goitre) is defined as thyroid enlargement not associated with thyroid dysfunction or malignancy(50). Further sub-classified based on the presence of nodular elements is also possible. Goitre may also be associated with hyperfunction either due to diffuse hyperthyroidism such as associated with Graves' disease or functional autonomy such as occurs in long-standing multinodular goitre (toxic

multinodular goiter) that evolves through phases of diffuse enlargement, multinodular change and ultimately functional heterogeneity between nodular areas. (1, 21, 45, 46).

NODULAR THYROID DISEASE

General

Nodular thyroid disease and goiter are the most frequently encountered manifestations of thyroid disease (41, 54). They exhibit a slight female predilection, although age, iodine nutrition and family history are the most important modifiers of risk (21, 54, 55). In particular, the prevalence of goitre is largely determined by the adequacy of iodine nutrition (24, 45, 46, 52, 56). For example, in iodine deficient Jutland, goiter was present in 12.2% of females and 3.2% of males, whereas in the genetically similar but iodine sufficient Icelandic population the prevalence was 1.9% and 2.2% respectively(48). In iodine deficient communities goiter prevalence also varies depending on the severity of the deficiency and the presence of other goitrogenic factors(24-26).

Thyroid nodules are common in both iodine deficient and sufficient populations, the apparent prevalence of thyroid nodules greatly influenced by the mode of evaluation(41, 50, 57). The prevalence of a palpable thyroid nodules was 1.6% and 6.4% for men and women respectively in the Framingham study(58). Similarly, the Wickham study reported palpable nodules in 0.8% and 5.3% of men and women respectively(59). Unlike clinically apparent thyroid nodules, subclinical nodular thyroid disease is common(41). Ultrasonography is particularly sensitive, identifying nodules in approximately one third of adults, the prevalence increasing with age. Of note, even relatively large thyroid

nodules may be inapparent on clinical examination, with only 48% of ultrasonographically evident thyroid nodules >2cm being palpable (41, 50, 57). Furthermore, autopsy studies show prevalence of thyroid nodules to be even higher, ranging between 30-60%(60, 61).

Thyroid Imaging

Over the past two decades ultrasonography has been used increasingly as the primary modality for thyroid evaluation(41, 62, 63). Thyroid ultrasonography has the capacity to detect thyroid lesions as small as 2mm in diameter and has five-fold greater yield for identifying thyroid nodules than does palpation(53, 54, 57, 64, 65). High resolution ultrasonography with a transducer operating at frequencies between 7-13 MHz is typically used, providing good visualization of suprasternal thyroid tissue whilst accurately determining if thyroid nodules are solid or cystic (53, 62, 66). Volumetric assessment of overall thyroid and nodule size can be undertaken with a measurement error of 10-16%(50, 67). Limitations include lack of penetration through bone and air, making ultrasound an unsuitable modality for study of retrosternal thyroid tissue, and limited in ability to differentiate benign from malignant disease(53).

Thyroid nodules identified by ultrasonography can be described as hyperechoic (greater echogenicity than normal thyroid tissue), hypoechoic (lower echogenicity) and isoechoic (similar echogenicity)(50, 68). The majority of thyroid nodules are solid, the majority of which are hypoechoic, with a significant minority exhibiting some degree of cystic change(41, 53, 57). In many studies, nodule prevalence based on ultrasonography in approaches 50% of the adult population, with increasing age a key determinant of increased prevalence (41, 46, 50, 64, 69).

Sonographic features of nodules that indicate benignity include the presence of a simple cyst, an hyperechoic and homogeneous echotexture, limited intranodular vascular flow on Doppler, a regular margin, coarse calcifications, and a thin halo. (1, 50, 70). Although these criteria confer a low risk of malignancy, they cannot fully exclude malignancy (1, 53, 70). Given the high prevalence of thyroid nodularity in the general population and the inability of ultrasonography to exclude malignancy great potential exists to generate additional investigations when imaging studies such as ultrasonography are applied widely in an otherwise asymptomatic population(41, 50, 54, 71).

Other modalities such as computed tomographic (CT) scanning, magnetic resonance (MR) imaging and thyroid scintigraphy may also identify thyroid nodules(41, 50, 71). Thyroid scintigraphy using either Technetium 99 pertechnetate or radioiodine can classify nodules according to their functional status. Whilst thyroid malignancies are almost always hypofunctioning or isofunctional, the majority (>75%) of thyroid nodules exhibit this appearance, yet only a minority (8-25%) of such nodules harbour malignancy(46, 50).

Like ultrasonography, MR and CT imaging provides structural information regarding thyroid size, nodule number and characteristics. In addition they are a useful modality for assessment of retrosternal thyroid tissue and have some advantage over ultrasound with regard to reduced inter-observer variation for volumetric assessment of goiter size(50). However, they are not superior to ultrasonography for characterizing malignant potential. Thyroid ultrasonography is not only simpler and more cost effective, but it is

generally a more sensitive tool for evaluation of structural thyroid disease(2, 41, 53, 67). The role positron emission tomography (PET) imaging in the evaluation of thyroid malignancy is limited by technique availability, cost and radiation exposure. However, PET has been demonstrated to be a sensitive and specific modality for identifying malignant thyroid lesions(50).

INVESTIGATION OF THYROID NODULES

Evaluation of the patient with nodular thyroid disease has changed over the past three decades, largely reflecting the increased use of both TSH and fine needle aspirate biopsy (FNAB) in the initial work-up of patients with nodular thyroid disease(50, 65, 72-74). Current recommendations suggest an initial measurement of TSH, which, if suppressed, should be followed by an evaluation of thyroid autonomy/hyperfunction using an assessment of peripheral thyroid hormones and thyroid scintigraphy(50, 73, 75, 76).

In those individuals with a dominant or otherwise suspicious lesion and a normal TSH (which represents the majority of patients with incidentally discovered thyroid nodules), FNAB for cytological evaluation is generally recommended(50, 76, 77). This approach is aimed at excluding thyroid carcinoma and stratifying patients into low risk and high-risk categories. Patients at low *a priori* clinical risk with normal FNAB results can avoid surgical biopsy/ thyroidectomy(50, 78). Those individuals with suspicious or overtly malignant aspirates are referred for surgical resection of the nodule(50, 75, 76). This may involve either unilateral lobectomy or total thyroidectomy depending on whether malignancy is identified(50, 76). A proportion of individuals have non-diagnostic

aspirates, which contain insufficient thyroid cellular elements, and repeat biopsy or surgical excision is usually recommended (74, 76, 79).

FNAB is undertaken using a 21-25 gauge needle(1, 2, 74, 80, 81). Between three and five aspirates are taken from the nodule, with each specimen containing at least five or six groups of ten to fifteen cells(74, 82). Palpable nodules may be amenable to biopsy without ultrasonographic guidance, although impalpable and incidentally discovered nodules frequently undergo biopsy using ultrasound-guided techniques(81, 83, 84). Adequate aspirates are often reported as either benign, indeterminate/suspicious or malignant(72, 74, 79, 83). In general, studies report malignancy in 5%, suspicious cytology in 10%, benign features in 70% and unsatisfactory sampling in 15% of patients undergoing FNAB(50, 72, 74, 79, 81). Ultrasound-guidance for FNAB improves the success rate for adequate sampling, particularly in lesions with a cystic component(85, 86).

The diagnosis of TC can be made on FNAB with a high degree of sensitivity and specificity(72, 87). The false negative rate for a benign aspirate is considered to be approximately 1-5% (50, 76, 88). Similarly, false positive cytological diagnosis of malignancy is relatively low in the range of 5%(88, 89). However, difficulty can arise in relation to aspirates consistent with a follicular neoplasm. Resection is recommended as these may represent either a follicular adenoma or malignancy (50, 72, 76, 79, 90).

Where the diagnosis of TC is uncertain preoperatively, and histological confirmation is required, tumour resection by unilateral lobectomy with intra-operative frozen section

histopathology may be used (72, 76, 91). In such cases, patients with clearly benign lesions need not proceed to total thyroidectomy, whilst those with carcinoma can be definitively treated at the time of initial surgery. In other cases, particularly for PTC, where diagnosis of carcinoma is made by histopathology on the paraffin embedded specimen, completion thyroidectomy is usually undertaken within a few days or weeks of the initial unilateral resection(76, 92, 93).

PAPILLARY THYROID CARCINOMA

General

Thyroid cancer is the most common endocrine malignancy, accounting for approximately 1% of total malignant diagnoses recorded by cancer registries(94-96). Four broad categories of thyroid cancer account for the majority of diagnoses – papillary (PTC), follicular (FTC), medullary (MTC) and anaplastic (ATC) (1, 2, 97). Depending on study methodology and geographic region, 50-90% of all diagnoses are PTC, followed by FTC, with other histotypes accounting for less than 15% (98-104). With the exception of MTC which arises from the C-cell elements of the thyroid, PTC, FTC and many ATC arise from the epithelial elements which give rise to the thyroid follicle(1, 2, 97). TC annual incidence ranges from 3-7 per 100 000 in most countries, however a wide variation in incidence rate is reported, both between geographic areas as well as within the same locality over time(94-96). In particular, the annual incidence of thyroid cancer in many countries has increased by over 50% in recent decades(94-96).

Classification

The current World Health Organisation (WHO) classification of PTC recognises 15 morphological subtypes, including tall cell, columnar and follicular variants(105). An important revision to the current scheme was undertaken in 1988 (97, 105-108). After this time, the classification mandated any thyroid carcinoma displaying papillary features, whether as a dominant morphology or in conjunction with other elements (such as follicular development), be classified PTC(97, 105). This has the potential to inflate the apparent occurrence of PTC verses FTC. Similarly, the incidence of FTC may have increased due to the contemporary classification of minimally invasive FTC, an entity that previously may have been assigned a diagnosis of follicular adenoma(108).

Molecular Pathogenesis

The genesis of PTC appears to be that theorized for other carcinomas in which successive mutations involving growth regulating genes lead to the ultimate development of a malignant phenotype(109-113). A progression through the sequential steps of hyperplasia, benign adenoma and ultimately, carcinoma has been postulated, although there is paucity of evidence to suggest benign thyroid neoplasms (follicular adenoma) undergo malignant transformation(46, 114). Whilst the thyroid gland is particularly prone to developing hyperplastic nodules, these *per se* do not appear to increase significantly the risk of PTC(21, 46).

A number of genes are linked to the development of PTC, including *RAS*, *Ret/PTC*, *TRK*, *BRAF*, *p53*, *MET* and *PAX8*(49, 109, 110, 115-117). The initial molecular genetic alterations in PTC pathogenesis are poorly characterized, although activation of the MAP kinase pathway (which influences cell proliferation and survival) by *BRAF* mutations

appear important (109, 118). Of particular interest are *ret*/PTC mutations. Fusion of *RET* to the promoter region of an unrelated gene gives rise to these mutations collectively termed *ret*/PTC rearrangements(119). This chimeric oncogene results from activating mutations involving *RET* (a proto-oncogene encoding a receptor tyrosine kinase) that may arise after thyroidal irradiation(115, 120-125). The most prevalent of these are *RET/PTC1* and *RET/PTC3*(119, 126, 127). Both mutations result from inversions involving the long arm of chromosome 10. High levels of radioiodine fallout following the Chernobyl accident produced an early and overt rise in childhood PTC associated with the *RET/PTC3* rearrangement(115, 121).

Subsequent studies have also shown *RET/PTC1* to be associated with adult PTC developing after radiation exposure, particularly those associated with PTC developing after long latency (>10 years) following childhood exposure to radioiodine fallout(115, 116, 119, 124, 128). Of note, studies following the Chernobyl accident indicate that whilst *RET/PTC3* was three fold more common than *RET/PTC1* in the first decade after irradiation, this ratio was reversed in PTC diagnosed after a long (>10 year) latency from radioiodine exposure (115, 124). The *RET/PTC1* rearrangement has also been associated with tumour behaviour and prognosis, some studies suggesting an association with a relatively benign clinical pattern of disease(111, 117, 119, 129, 130).

Ionising Radiation

Only ionising radiation has a well established exposure-risk relationship for TC (131-135). The dominant malignancy arising after thyroid irradiation is PTC. Both ingestion of radioiodine and external beam exposure are linked to thyroid cancer(133-136). It is recognised that the latency between radiation exposure and the development of thyroid

cancer can span decades(133, 135). Whilst there exists no apparent threshold for induction of thyroid neoplasia, the risk is greatest when exposure to ionizing radiation occurs during early childhood, the resultant carcinoma potentially presenting in adulthood. In the case of the Chernobyl reactor disaster, the exposed population experienced a substantial rise in childhood PTC within a decade, but the increased incidence persisted for many years thereafter, indicating that PTC may occur at both short as well as long latency after thyroidal exposure to radioiodine. (132, 133, 135, 137, 138).

Consequential to the Chernobyl reactor accident, it has been proposed TC incidence increased in locations as distant as Connecticut in the United States of America(139-141). Closer to the site of the disaster, in Belarus, substantial incidence increases in thyroid cancer have occurred in recent years(132, 134, 142, 143). Genetic susceptibility and baseline iodine nutrition appear to modulate thyroid cancer risk after ionising irradiation. Low levels of dietary iodine elevate thyroidal uptake of radioiodine, increasing neoplasia risk(144-146). Human thyroidal exposure to nuclear fallout is likely to be mediated by consumption of factors such as cows milk, which bio-accumulates radioiodine (144, 147, 148). Low-level exposure by this mechanism has the potential to affect large populations.

Whilst the magnitude of effect expected from low level radioiodine fallout is unclear, the possibility of some influence on population PTC epidemiology is supported both by data arising from the Chernobyl accident as well as the observations made following contamination of South Pacific islands by the Bikini Atoll weapons test (134, 139). By extrapolation, the linear dose response relationship, in conjunction with the absence of an

effect threshold and a protracted effect latency, suggests low level radioiodine fallout in conjunction with preexisting iodine deficiency may increase (albeit subtly) PTC incidence many up to years after the initial exposure (133, 134, 146). Conversely, studies to date in the populations affected by both the Nevada weapons tests and the Hanford event, have failed to show any convincing increase in thyroid malignancy(134). Further appropriately powered studies, with sufficient exposure data for participants, are needed to resolve this ambiguity(141, 149).

Familial Susceptibility

A number of familial syndromes are associated with an increased risk for follicular cell malignancy - familial polyposis coli, Cowden's syndrome and Peutz-Jaegers syndrome(96, 150). These syndromes result from genomically diverse mutations, providing further indication of multiple loci for genes involved in regulating thyrocyte growth. In addition, familial PTC with an autosomal dominant inheritance pattern is increasingly reported (96, 151-156). Loci for papillary carcinoma and familial non-medullary thyroid carcinoma have been suggested for chromosome 14q31 and chromosomes 3 and 8 (translocation) (157, 158). Present data suggest familial autosomal dominant PTC is likely to be a genetically heterogeneous disorder, with potential phenotypic overlap with benign nodular goiter(159). Identification of families at increased risk of PTC offers the potential to offer pre-symptomatic screening and improve prognosis (160).

Iodine Nutrition

The relationship between iodine nutrition and thyroid carcinoma pathogenesis is

complex. Epidemiological data show a trend for TC rates to be greater in populations with higher iodine intake (25, 27, 29, 131, 161-163). Of note, despite similar genetic backgrounds, Iceland (which has a high iodine intake) has a TC rate four-fold that of

Denmark where iodine intake is lower(95, 164). It has been observed that FTC and anaplastic thyroid carcinoma occur relatively more frequently in iodine deficient populations, whereas PTC is more dominant in areas of iodine sufficiency(161, 165). However, this is not a universal finding as high rates of PTC can be found in both iodine deficient and iodine sufficient populations. Nonetheless, there is a tendency to higher PTC rates in those populations that have the highest levels of iodine nutrition.

Improved iodine nutrition in previously iodine deficient communities has also been associated with increased PTC incidence(31, 163, 166). This effect, which has been called “papillarization”, and is characterised by an increase in the PTC : FTC incidence ratio, a fall in PTC size and an attenuation of malignant phenotype(28, 31). Of note, the increase in PTC following iodine supplementation is largely attributable to a rise in small lesions - tumours that generally have a good prognosis(167, 168). The biological mechanisms underlying this observation is unclear, however subtle changes in TSH secretion induced by improved iodine nutrition are a possible link. However, the relative contribution of improved health standards (resulting in increased thyroid evaluation) versus a true change in disease pathogenesis remains to be clarified (29, 168-170).

Incidental and Asymptomatic PTC (“occult” PTC)

Incidental diagnoses of TC are frequently made at autopsy and routine histopathology of

thyroid tissue resected for benign indications (171). Mortison *et al* in 1954 showed that 2.8% of thyroid glands from one thousand consecutive autopsies performed at the Mayo Clinic harbored TC (61). These tumours were not clinically evident antemortem. Careful histopathological evaluation of thyroid tissue resected for non-malignant indications can also result in the diagnosis of thyroid malignancy(172). Similarly, cytological evaluation of thyroid nodules incidentally detected during imaging of other neck structures may result in the detection of TC(173). Overall, prevalence estimates from surgical and autopsy series suggest an underlying rate of 5% in the adult population (41, 172, 174). The vast majority (>90%) of these tumours are PTC(60, 71, 172).

Papillary Microcarcinoma

Papillary microcarcinoma can be defined as a PTC of ≤ 1 cm in maximum dimension(175-177). The prevalence of papillary microcarcinoma is largely determined by the sensitivity of the screening process used for their identification. In one autopsy study, systematic fine sectioning and staining of thyroid specimens revealed a prevalence of 22% compared to 4.6% when a less sensitive macroscopic evaluation was used(178). Many lesions are smaller than 5mm in diameter (179).

Papillary microcarcinoma are frequently multicentric (93, 171, 174, 180). Approximately one third of patients with PTC can be shown to have more than one focus of carcinoma (93, 181). The likelihood of finding multicentric PTC is directly related to the acuity with which the thyroid tissue is examined, and does not appear related to clinical stage of the initial tumour (93, 181). Some will be coincidental "occult" PTC (given the high prevalence in a community of such lesions) but a proportion may represent a multicentric process originating from a common aetiological factor.

The origin of multifocal papillary thyroid carcinoma has been the subject of debate with two options proposed: either a multifocal process where tumours develop independently within the thyroid (possibly with an underlying predisposing factor), or tumours arising as metastases from one primary tumour (96, 111). The former appears to be the most common explanation, as studies have identified a range of different mutations suggestive of distinct clonality in tumours at different sites within the same thyroid gland (111).

A body of both direct and indirect information suggests that the biological behavior of “occult” papillary microcarcinoma is less aggressive than clinically evident and larger PTC (117, 176, 177). However, these tumours are not invariably “benign” in their behaviour, with some patients developing metastatic disease and a 1% disease specific mortality (93, 175, 176, 180, 182, 183). These tumours may form a pool of precursor lesions of which a minority ultimately acquire mutations that allow progression to aggressive growth and metastases. Acquisition of growth dysregulating mutations by microcarcinoma may then result in progression to clinical disease(117). However, it appears many of these tumours remain asymptomatic, with a proportion undergoing spontaneous resolution.

CLINICAL ASPECTS OF PTC MANAGEMENT

Tumour Staging

A number of staging systems are used in relation to PTC. These include TNM, MACIS, AMES, AGES and EORTC (76, 184-186). These systems represent different attempts at accurately predicting prognosis, and adequately identify the 70-85% of patients in whom

disease specific mortality is unlikely (76). The TNM system is typical and often used by tumour registries. It comprises three elements –size of primary tumour (T), the presence or absence of regional lymph node metastases (N), and the presence or absence of distant metastases (M) (76). The anatomical extent of thyroid carcinoma can be effectively characterised by the TNM system with the classification based on data originating from either clinical (cTNM) or pathological (pTNM) information. The four stage groupings for differentiated TC, further incorporate age ≥ 45 or < 45 years into the classification scheme(184).

Surgical Management

Complete tumour excision is essential for the management of PTC (76). However, debate exists with regard to the role of total or near total thyroidectomy, as opposed to ipsilateral thyroid lobectomy, for low risk very small PTC (76, 96, 183, 185). Most authorities currently recommend total thyroidectomy for all PTC, although ipsilateral lobectomy and isthmusectomy is advocated in some circumstances for papillary microcarcinoma (76, 96). Completion thyroidectomy is usually undertaken in patients in whom a unilateral lobectomy for a non-malignant indication reveals PTC (76). An important benefit of total thyroidectomy relates to the frequent occurrence of multifocal PTC that involves not only the ipsilateral but also the contralateral lobe. Furthermore, total thyroidectomy is an important prelude to radioiodine ablation and subsequent thyroglobulin based follow-up protocols (76, 187).

Damage to the recurrent laryngeal nerve and permanent hypoparathyroidism are the major complications of thyroidectomy (101, 188, 189). Both should occur in less than 2% of patients (188, 189). Following total thyroidectomy, transient hypocalcaemia may

occur in as many as one quarter of patients (188). However, parathyroid function recovers in the majority of these individuals with time.

Radioiodine Ablation

Ablation of residual thyroid tissue and tumour is frequently recommended. I^{131} for differentiated thyroid carcinoma (PTC and FTC) has limited impact on surrounding tissue in comparison to deep x-ray therapy (76). However, debate surrounds the benefit of I^{131} treatment in improving prognosis for low risk tumours, particularly “occult” papillary microcarcinoma (76, 185). Nonetheless, radioiodine ablation has the benefit of eliminating residual normal thyroid tissue, making thyroglobulin a sensitive marker of tumour recurrence (76, 187). Patients receiving I^{131} require an appropriate degree of TSH stimulation of neoplastic and residual normal thyroid tissue (76). This is achieved by either thyroid hormone withdrawal for up to six weeks or use of recombinant TSH prior to administration of radioiodine.

Surveillance

Long term follow-up of patients with PTC is required (76, 92). Optimal management requires TSH suppression, monitoring of serum thyroglobulin and periodic ultrasonographic neck imaging (76, 92, 187). In some cases additional imaging using conventional imaging, radionuclide scintigraphy or positron emission tomography is required (76). The frequency of follow-up and the modality used is determined by the clinical situation and the prognostic category of the carcinoma (76, 187).

Prognosis

The prognosis of PTC is generally excellent (76, 185, 190). The vast majority (>90%) of patients diagnosed with PTC are effectively rendered disease free by thyroidectomy and radio-iodine ablation (76, 92, 185, 186, 191). Most patients have stage 1 disease for

which long term disease free survival exceeds 95% (183, 186). Papillary microcarcinoma (particularly “occult” disease) has an excellent prognosis with a cause specific mortality of <1% (175, 176, 183). Later stage, older age at diagnosis and male gender are associated with a higher risk of disease recurrence and PTC related mortality (186, 191).

Disease related mortality is often a result of pulmonary metastases or local aero-digestive invasive disease. However, disease recurrence is frequently treated effectively by surgical resection and radioiodine (76). The risk of recurrence is greatest within the first decade following initial treatment and is also higher in the those individuals aged under 20 years and over 60 years at the time of initial diagnosis(191). Mortality rates are lowest in patients aged under 40 years rising with increasing age over 40 years (191). The mortality rate for PTC at 25 years post treatment is approximately 5% whilst tumour recurrence is 14% (185, 191).

GLOBAL INCIDENCE PATTERNS FOR PTC

Geographic Distribution and Ethnic Susceptibility

The absolute incidence of TC varies significantly between geographic locations. Some of the highest incidence rates are recorded in Iceland and the Philippines, whilst the United Kingdom and New Zealand report amongst the lowest (Table 1.1)(94, 95, 164). A significant correlation between ethnicity, independent of country of residence, is also seen (Table 1.2) (94, 95, 164). For example, ethnic Filipino residing in Hawaii have TC incidence rates which are more than two fold higher than those occurring amongst ethnic

Japanese and Chinese in the same community (94, 95, 164, 192). Interestingly, Hawaii has higher rates of thyroid carcinoma for each of these ethnic subgroups than is observed for the same ethnic groups living on the North American mainland (Table 1.2) (94, 95, 164, 192). Given the relative comparability of health care between locations, these divergent results at different geographic sites suggest environmental as well as genetic factors play a role in the pathogenesis of TC.

Temporal Trends

Aside from differences between communities for absolute incidence, a significant temporal increase has occurred for the incidence of TC within many communities over recent decades. Substantial increases have occurred in both industrialised and developing nations, as well as in places as geographically diverse as Australia, the United States and Europe (Table 1.1, 1.2, 1.3) (94, 95, 164). This change is notably evident for PTC, whereas there has been little apparent alteration in the incidence of other carcinoma subtypes. Incidence rates for PTC have risen (in some cases by over 400%) during the past half-century (96, 98, 103, 131, 140, 193-199). The rise in TC incidence has occurred in a variety of jurisdictions with varying ethnic backgrounds (Table 1.1, 1.2) (94, 95, 164).

Longitudinal data collected by national registries is susceptible to biased case ascertainment (200, 201). Length bias, lead time bias and variation in the completeness of case registration all contribute (71, 201). Length bias is particularly relevant to PTC (71, 201). As the prevalence of clinically overt PTC is less than 0.1% and “occult” papillary microcarcinoma is detectable in 0.45-13% of adults from the general population, any increase in the utilisation of ultrasonography, particularly ultrasound

guided FNAB of non-palpable nodules, is likely to result in increased diagnosis of “occult” PTC (41, 71, 84, 141, 168, 179, 196, 202, 203). If the entire pool of occult PTC were identified antemortem, the resulting ascertainment bias could alone result in a 50-fold rise in the apparent incidence of PTC (16, 17, 18, 21, 61, 71, 174, 204, 205).

Table 1.1 Global comparison of age standardised rates for thyroid cancer and the relative change in rates between 1983-1987 and 1993-1997.

Country	ASR (1983-87)		ASR (1993-97)		ASR Relative Δ	
	Male	Female	Male	Female	Male	Female
Iceland	6.2	8.3	4.3	12.6	-30.7	51.8
Manila	3.5	8.6	2.9	9.7	-17.1	12.8
Belarus	0.6	1.9	2.3	8.5	283.3	347.4
USA (white)	2.2	5.8	2.8	7.7	27.3	32.8
Hong Kong	1.5	5.7	1.9	7.1	26.7	24.6
Canada	1.7	4.3	2.1	6.4	23.5	48.8
NSW & Vic	1.3	3.2	2.0	5.6	53.9	75.0
Norway	1.6	5.1	1.5	4.3	-6.3	-15.7
USA (black)	1.0	2.7	1.4	4.0	40.0	48.2
Shanghai	0.9	2.2	1.1	3.8	22.2	72.7
St Petersburg	1.1	2.9	1.3	3.8	18.2	31.0
New Zealand	1.1	3.0	1.7	3.5	54.6	16.7
Sweden	1.6	3.8	1.3	3.5	-18.8	-8.6
Denmark	1.0	2.0	1.0	2.3	0.0	15.0
Ireland	1.0	2.2	0.9	1.9	-10.0	-13.6
UK	0.7	1.5	0.8	1.9	14.3	26.7

Data derived from "Cancer Incidence in Five Continents", Volumes VI and VIII, IARC Press, Lyon, France. Parkin DM, Whelan SL, Ferlay J et al (eds). Cancer incidence in five continents Vol VIII. IARC Sci Publ 5, Lyon, 2002.

Parkin DM, Muir CS, Whelan SL et al (eds). Cancer incidence in five continents Vol VI. IARC Sci Publ 5, Lyon, 1992.

Table 1.2 Ethnic comparison of age standardised rates for thyroid cancer and the relative change in rates between 1983-1987 and 1993-1997.

Ethnic Background	ASR (1983- '87) (Case/100000)		ASR (1993-'97) (Case/100000)		ASR Relative Δ (%)	
	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>
Scandinavian						
Iceland	6.2	8.3	4.3	12.6	-30.7	51.8
Sweden	1.6	3.8	1.3	3.5	-18.8	-8.6
Denmark	1.0	2.0	1.0	2.3	0.0	15.0
Chinese						
Hong Kong	1.5	5.7	1.9	7.1	26.7	24.6
Hawaii	8.1	11.3	4.6	6.7	-43.2	-40.7
Los Angeles	2.0	3.1	1.7	6.1	-15.0	96.8
Shanghai	0.9	2.2	1.1	3.8	22.2	72.7
Filipino						
Hawaii	6.6	24.2	5.0	19.4	-24.2	-19.8
Los Angeles	4.6	7.9	5.0	12.1	8.7	53.2
Manila	3.5	8.6	2.9	9.7	-17.1	12.8
Japanese						
Hiroshima	1.9	5.6	2.1	10.5	10.5	87.5
Hawaii	4.3	6.3	1.9	7.3	-55.8	15.9
Los Angeles	1.4	6.9	1.6	4.8	14.3	-27.5
Anglo-Celtic						
Ireland	1.0	2.2	0.9	1.9	-10.0	-13.6
UK	0.7	1.5	0.8	1.9	14.3	26.7

Data derived from “Cancer Incidence in Five Continents”, Volumes VI and VIII, IARC Press, Lyon, France.
 Parkin DM, Whelan SL, Ferlay J et al (eds). Cancer incidence in five continents Vol VIII. IARC Sci Publ 5,
 Lyon, 2002.

Parkin DM, Muir CS, Whelan SL et al (eds). Cancer incidence in five continents Vol VI. IARC Sci Publ 5,
 Lyon, 1992.

Table 1.3 Australian comparison of age standardised rates for thyroid cancer and the relative change in rates between 1983-1987 and 1993-1997.

Location	ASR (1983- '87) (Case/100000)		ASR (1993-'97) (Case/100000)		ASR Relative Δ (%)	
	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>	<i>Male</i>	<i>Female</i>
NT	na	na	1.3	6.4	-	-
New South Wales	1.3	3.6	2.2	6.3	69.2	75.0
Tasmania	1.0	3.4	1.9	6.0	90.0	76.5
Queensland	na	na	1.9	5.8	-	-
Western Australia	1.4	3.7	1.5	5.0	7.1	35.1
South Australia	1.0	3.4	1.8	5.0	80.0	47.1
ACT	1.1	6.8	1.4	4.4	27.3	-35.3
Victoria	1.3	2.7	1.6	4.3	23.1	59.3

Data derived from “Cancer Incidence in Five Continents”, Volumes VI and VIII, IARC Press, Lyon, France.
 Parkin DM, Whelan SL, Ferlay J et al (eds). Cancer incidence in five continents Vol VIII. IARC Sci Publ 5, Lyon, 2002.

Parkin DM, Muir CS, Whelan SL et al (eds). Cancer incidence in five continents Vol VI. IARC Sci Publ 5, Lyon, 1992.

CHAPTER 2

Temporal trends for thyroid carcinoma in Australia: a rising incidence of papillary thyroid carcinoma (1982 – 1997).

Prologue

The key questions addressed in this chapter are:

- 1 Has PTC incidence increased in Australia?
- 2 Are patterns of PTC incidence uniform across Australia?

Presentations and publications arising from this Chapter:

Presented

Preliminary results presented at the International Congress of Endocrinology (ICE 2000), Sydney, Australia, 2000.

Published

Burgess JR. 2004 Temporal trends for thyroid carcinoma in Australia: an increasing incidence of papillary thyroid carcinoma (1982-1997). *Thyroid* 12:141-9.

In accordance with the criteria for submission of thesis by previously published research, Chapter 2 is based on the above cited publication.

Aim

- 1 To evaluate TC incidence trends in Australia, with particular reference to PTC incidence.
- 2 To determine if Tasmanian TC incidence trends are representative of Australian national incidence patterns.
- 3 To assess the possible role of ascertainment bias and changes in risk factor exposure on TC incidence trends.

Hypothesis

- 1 Increasing TC incidence in Australia is due to increased diagnosis of PTC.
- 2 The Tasmanian population is an appropriate model for evaluating factors underlying thyroid carcinoma incidence trends in Australia.

Introduction

Thyroid carcinoma (TC) is the most commonly encountered endocrine malignancy(94, 95). Papillary thyroid carcinoma (PTC) is the most prevalent of the TC subtypes (98, 194, 199, 206). Longitudinal data from population based cancer registries shows the incidence of PTC to have risen up to five-fold in a number of countries over the past six decades (94, 96, 98, 194). The explanation for this remains unclear(203, 207-209). Potential causes include increased ascertainment of “occult” papillary microcarcinoma as well as changing exposure to risk factors such as ionising radiation and iodine nutrition(203, 208-210).

In Australia, state based Cancer Registry data also indicate TC incidence has increased during past two decades(94, 95, 164). Whilst previously published national data have not specifically evaluated trends for PTC, an hospital based study from New South Wales by Fahey *et al* suggested there had been an increase in the underlying incidence of PTC (210). A detailed analysis of national TC incidence trends, with particular reference to PTC incidence, is now required to evaluate the changes in TC incidence observed elsewhere in Australia.

This report examines PTC incidence trends throughout Australia during the period 1982 - 1997.

Subjects and Methods

Australia comprises six States [Queensland (QLD), New South Wales (NSW), Victoria, Tasmania, South Australia (SA) and Western Australia (WA)] and two relatively less populated Territories. QLD, NSW, Victoria and Tasmania are on Australia's eastern seaboard, whilst SA and WA are located to the mid south and far-west respectively of the Australian continent.

By statutory regulation cancer registries in each State and Territory collect data on all diagnoses of cancer (excluding non-melanoma skin cancer). All public and private pathology facilities participate in the cancer registry program. Nationwide data is subsequently collated by the Australian National Cancer Statistics Clearing House. As of January 2001 a full data set for the entire Australian population was available for the period 1982 - 1997.

Following Institutional Ethics Committee approval, the Australian National Cancer Statistics Clearing House provided de-identified case data on all diagnoses of thyroid carcinoma occurring in Australia between 1982 and 1997. Cases were assigned to one of four histopathologic categories; PTC, FTC, MTC, and ATC. There were additional minority diagnoses ("other diagnoses"). "Other diagnoses" is a heterogeneous grouping containing other tumours for which thyroid was registered as the primary site. The dominant components were Hurthle cell malignancy (26%) and "carcinoma not otherwise specified" (NOS) (18%). The remainder of this grouping comprised multiple diagnosis codes, some of which may represent incorrect classifications. It was not possible to further evaluate this from the data available.

Age standardised incidence rates (ASR) were estimated using the world standard population age and gender weights, and are expressed per 100 000 of population(211). Normally distributed variables were analysed using the Student's t-test. Time trends in incidence rates were analysed by linear regression of the rates on year at diagnosis. Where appropriate, numerical data is presented as Mean \pm Standard Error of Mean (SEM).

Results

During the period 1982 – 1997 there were 9053 new diagnoses of TC in Australia. The overall female to male ratio was 2.68 and the median year for TC diagnosis was 1992. Of the TC categories PTC, FTC, MTC, ATC and “other diagnoses” accounted for 65.8%, 17.8%, 4.6%, 1.3% and 10.5% of cases respectively.

The age standardised incidence rate for all TC combined increased from 2.889 per 100 000/year to 5.522 per 100 000/year for females ($p<0.001$) and 1.272 per 100 000/year to 2.039 per 100 000/year for males ($p<0.001$) (*Table 2.1, 2.2, Figure 2.1*) over the study period. TC incidence rates increased by 6.7% per year for females and 4.4% per year for males between 1982-1997 ($p<0.001$). The increase was primarily due to a 10.7% per year ($p<0.001$) and 8.3% per year ($p<0.001$) rise in PTC incidence for females and males respectively (*Table 2.1, 2.2, Figure 2.1, 2.2*). The incidence of remaining species of TC did not change appreciably between 1982-1997 (*Table 2.1, Figure 2.2, 2.3*). The median age at diagnosis with PTC increased during the study period from 38 and 42 years to 43 and 46 years for females and males respectively (*Table 2.1*). The female to male incidence ratio did not change significantly over the study period (*Table 2.1*).

The proportion of patients with the follicular variant of PTC (fv-PTC) did not increase disproportionately relative to other PTC subtypes during the period of study (*Table 2.1, Figure 2.4*). PTC was observed to increase in all Australian States, however, the rise was most marked in the four eastern Australian states (Tasmania, QLD, Victoria and NSW) (*Table 2.2, Figure 2.5*). The greatest increase in incidence (24.7% per year) was observed in Tasmania ($P<0.001$) (*Table 2.2, Figure 2.5*).

Survival at two-, five and ten- years following PTC and FTC diagnosis improved progressively during the study period (*Table 2.1*). Survival for PTC and FTC improved in parallel (*Table 2.1*). In particular, the fatal incidence ratio (the ASR for patients dying within two years of diagnosis expressed in relation to the total ASR) for PTC decreased between 1982 - 1991 but remained relatively constant thereafter. A similar trend was observed for the FTC fatal incidence ratio.

Discussion

Whilst the incidence of PTC has increased in Australia during the past two decades, that of non-PTC thyroid malignancy did not change appreciably (*Table 2.1, Figure 2.1, 2.2, 2.3*). The increase in PTC is evident for both males and females, although the underlying differential in PTC incidence between genders is preserved (*Table 2.1, Figure 2.2, 2.3*). The rise in PTC may relate to two factors - a true increase in PTC incidence as well as the aggregate effect of biases arising from changes in clinical and diagnostic practice.

Ultrasonography, FNAB and detailed histopathologic examination of benign thyroidectomy specimens can contribute to over-diagnosis of “occult” PTC (60, 71, 201, 202, 204). It has been demonstrated that 30-50% of the adult population have ultrasonographic evidence of one or more thyroid nodules, the majority of which are asymptomatic and non-palpable lesions of no more than 1cm diameter(41, 57, 66). However, approximately 5% of such nodules represent “occult” papillary microcarcinoma. Although many of these lesions remain clinically irrelevant, once identified, most are subject to FNAB and surgical resection(60, 72, 75, 201).

Whilst FNAB is a useful and minimally invasive method for estimating the risk of malignancy, 5-15% of all FNAB are reported as either cytologically malignant or high risk thereof(72, 212). It might therefore be expected that one case of PTC will be diagnosed for every 20 non-palpable and asymptomatic thyroid nodules identified by ultrasound and subsequently evaluated by FNAB. Given ultrasound guided FNAB of small ($\leq 1\text{cm}$), non-palpable intrathyroidal nodules is becoming increasingly utilised, the potential for over-diagnosis of “occult” and clinically irrelevant PTC is great(41, 71).

Whether the initial identification of an “occult” PTC occurs serendipitously at the time of neck ultrasonography for a non-malignant indication, or during careful histopathologic examination of a thyroidectomy specimen, the majority of these neoplasms are not destined to produce clinically relevant disease or impact on life expectancy(41, 71, 201). Unfortunately, most cancer registries do not directly collect data on tumour size and clinical presentation. It is therefore not possible from the available data to determine the degree to which increased identification of small and “occult” PTC has influenced overall PTC incidence rates in recent decades.

Australian national trends for thyroid ultrasonography and FNAB have not been characterized adequately. However, the study by Fahey *et al* reported a rise in the number of PTC treated at a Sydney hospital over recent decades(210). The rise appeared equally attributable to an increase in both diagnosis of “occult” PTC as well as clinically relevant PTC(210). Extrapolation of this data to the national level would suggest at least half of the rise observed in Australian PTC incidence could be explained by increased use of ultrasonography and sensitive histopathological techniques(210, 213).

Indirect evidence against ascertainment bias as the sole cause for the rise in PTC incidence observed in Australia can be found in trends for PTC mortality. Despite a rise in the incidence of PTC versus FTC, parallel improvement in two-, five- and ten- year mortality rates have occurred. As “occult” PTC usually have a benign natural history, if PTC incidence had increased only due to greater recognition of “occult” PTC, a disproportionate improvement in survival for patients with PTC relative to FTC would be expected.

In particular, increased diagnosis of “occult” PTC should be manifest as a fall in the ratio of PTC fatal incidence : total PTC incidence. A decline in this ratio is evident between 1982-1991. However, during more recent years, particularly during the period of peak PTC incidence (1993-1997) the ratio remained stable. The initial decline between 1982-1991 could relate to either improved standards of patient care or ascertainment bias. However, given a similar trend is evident for the FTC fatal incidence ratio, improved management seems the likely explanation. Appreciation of the importance of total/ near-total thyroidectomy for PTC in the 1980's may account for this.

It has also been suggested that changes in diagnostic criteria, with reclassification of follicular tumours to fv-PTC might account for an apparent rise in incidence of PTC(106, 107). This is not borne out in the Australian data. Whilst fv-PTC incidence has increased, this rise only partly accounts for the observed overall increase in PTC rates (*Table 2.1, Figure 2.4*).

Marked variation in PTC incidence is evident between the Australian states (*Table 2.2, Figure 2.5*). The eastern Australian states have experienced a highly significant increase in annual PTC incidence, almost triple that of SA and WA (*Table 2.2, Figure 2.5*). As standards of health care in Australia are equivalent across states, the magnitude of ascertainment bias for contemporaneously incident tumours should be similar throughout Australia. Comparison of incidence trends between geographic regions ought therefore be valid.

The greatest relative and absolute rise in PTC incidence occurred in Tasmania (*Table 2.2, Figure 2.5*) (26). Whilst Tasmania is the most iodine deplete state in the Australia, it appears that much of the Australian eastern seaboard is also to varying extents ecologically iodine deficient. It is therefore interesting to note the greatest rise in PTC incidence outside Tasmania has also occurred in the intrinsically iodine deficient eastern states (*Figure 2.5*).

Conclusion

The incidence of PTC has increased throughout Australia during the past two decades. A differential increase in PTC favouring higher rates in geographic regions at greatest risk of iodine deficiency is evident. Greater identification of prevalent, yet clinically “occult” PTC may account for part of the observed increase, however a failure to observe an ongoing improvement in patient survival despite rising PTC incidence suggests an increase in incidence of clinically significant disease has also occurred. This may be linked directly or indirectly to population iodine nutrition or prior exposure to risk factors such as ionising radiation.

Further studies are required to 1) to confirm the accuracy of cancer registry case ascertainment, 2) to assess temporal trends for factors antecedent to the diagnosis of “occult” PTC, and 3) to seek evidence of geographic or temporal variation in PTC risk factor prevalence. Evaluation of these issues might be undertaken using the Tasmanian population as a model, given its stable demographic structure, and representative trends for PTC incidence.

**Table 2.1 Characteristics of thyroid carcinoma diagnosed in Australia 1982-
1997**

Year of Diagnosis	PTC		FTC	MTC	ATC	Other
	<i>PTC(all)</i>	<i>fv-PTC</i>				
1982-‘85						
Number of cases	906	288	338	65	24	256
Female (F):Male (M) ratio	2.76	3.30	2.76	1.50	3.00	1.91
F/M Median age (y)	38 / 42	42 / 48	47 / 54	58 / 44	69 / 63	64 / 61
F/M Incidence (ASR)	1.89 / 0.70	0.64 / 0.20	0.69 / 0.27	0.10 / 0.07	0.04 / 0.02	0.42 / 0.26
F/M 2-year survival (%)	92.0 / 88.4	93.2 / 92.5	89.1 / 83.3	84.6 / 76.9	0.0 / 0.0	51.8 / 48.9
1986-‘89						
Number of cases	1111	236	370	104	29	192
Female (F):Male (M) ratio	2.75	2.69	2.90	1.54	1.64	2.55
F/M Median age (y)	39 / 47	41 / 49	46 / 51	49 / 56	65 / 66	64 / 64
F/M Incidence (ASR)	2.17 / 0.80	0.46 / 0.17	0.71 / 0.25	0.15 / 0.11	0.04 / 0.03	0.29 / 0.14
F/M 2-year survival (%)	96.1 / 88.2	97.0 / 87.5	94.9 / 91.6	87.3 / 85.4	16.7 / 9.1	53.6 / 57.4
1990-‘93						
Number of cases	1594	306	415	123	29	244
Female (F):Male (M) ratio	3.29	4.19	2.58	1.05	2.22	1.68
F/M Median age (y)	42 / 47	41 / 47	49 / 59	55 / 54	77 / 63	61 / 67
F/M Incidence (ASR)	3.23 / 0.91	0.61 / 0.14	0.72 / 0.28	0.15 / 0.14	0.03 / 0.02	0.32 / 0.21
F/M 2-year survival (%)	96.6 / 88.4	97.2 / 90.0	95.0 / 90.5	87.3 / 80.0	30.0 / 0.0	70.5 / 59.3
1994-‘97						
Number of cases	2354	539	489	120	39	251
Female (F):Male (M) ratio	3.00	3.46	2.76	1.03	1.29	2.64
F/M Median age (y)	43 / 46	41 / 46	47 / 52	49 / 56	74 / 68	62 / 65
F/M Incidence (ASR)	4.09 / 1.35	0.97 / 0.28	0.82 / 0.29	0.14 / 0.14	0.03 / 0.03	0.36 / 0.15
F/M 2-year survival (%)	97.5 / 91.2	98.8 / 95.9	94.0 / 91.5	88.5 / 17.0	9.1 / 11.8	68.7 / 53.6

**Table 2.2 Statistical characteristics of total thyroid carcinoma and PTC diagnosed in
Australia 1982-1997**

Subgroup	Average annual Increase (%)	Confidence Interval		R ²	P =
		Lower 95%	Upper 95%		
Australian total TC					
Female	6.7	5.0	8.3	0.85	<0.001
Male	4.4	2.9	5.8	0.75	<0.001
Australian PTC					
Female	10.7	8.6	12.8	0.82	<0.001
Male	8.3	6.1	10.5	0.82	<0.001
PTC by State (M+F)					
Tasmania	24.7	17.8	31.6	0.81	<0.001
QLD	14.1	10.2	18.0	0.81	<0.001
Victoria	13.2	10.5	15.9	0.89	<0.001
NSW	10.1	8.0	12.2	0.89	<0.001
WA	5.8	2.7	8.9	0.54	=0.001
SA	4.0	1.4	6.5	0.44	=0.005

Figure 2.I Thyroid carcinoma incidence in Australia (1982 - 1997)

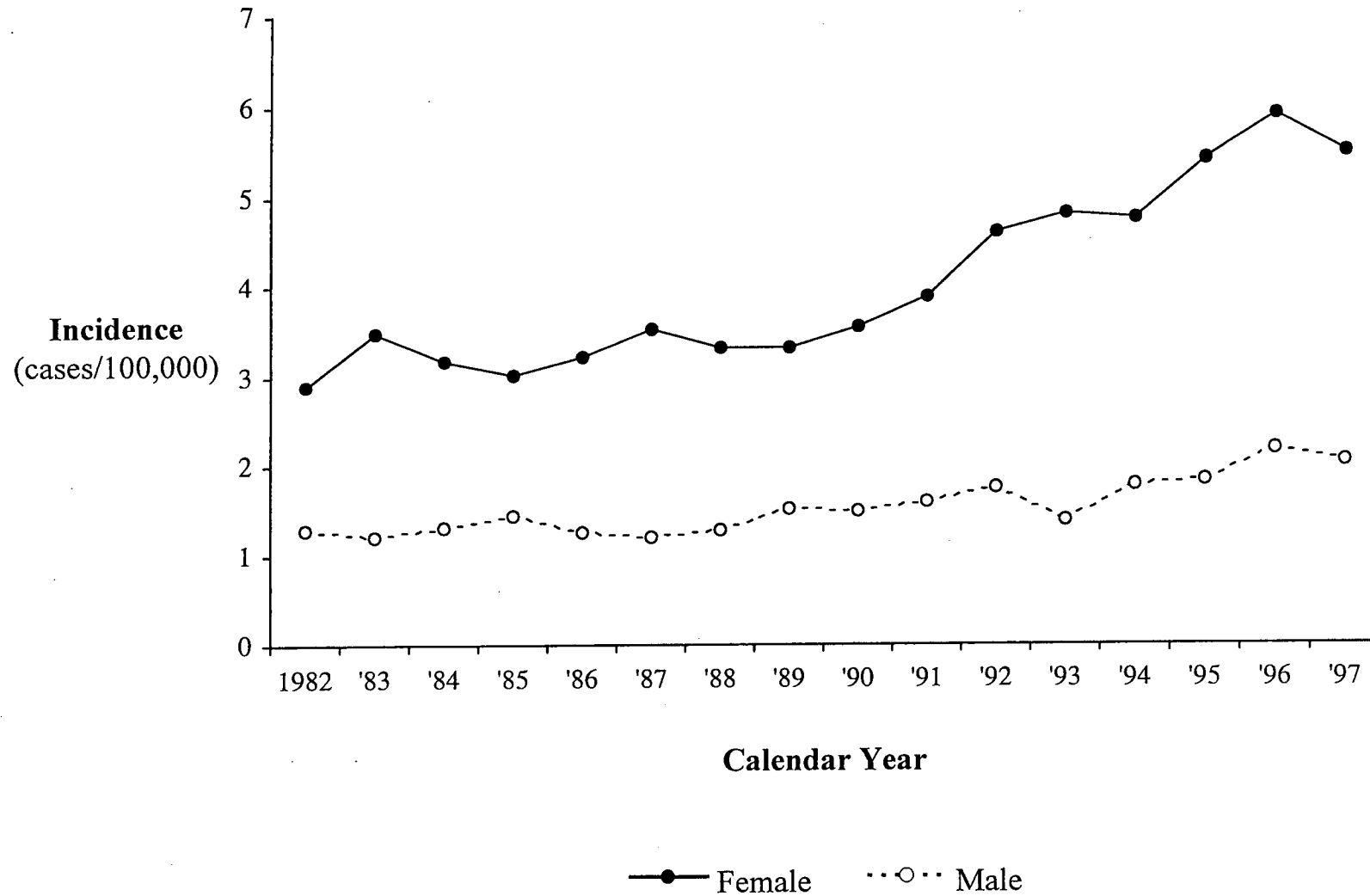


Figure 2.2 Thyroid carcinoma subtype incidence in Australia - females (1982 - 1997)

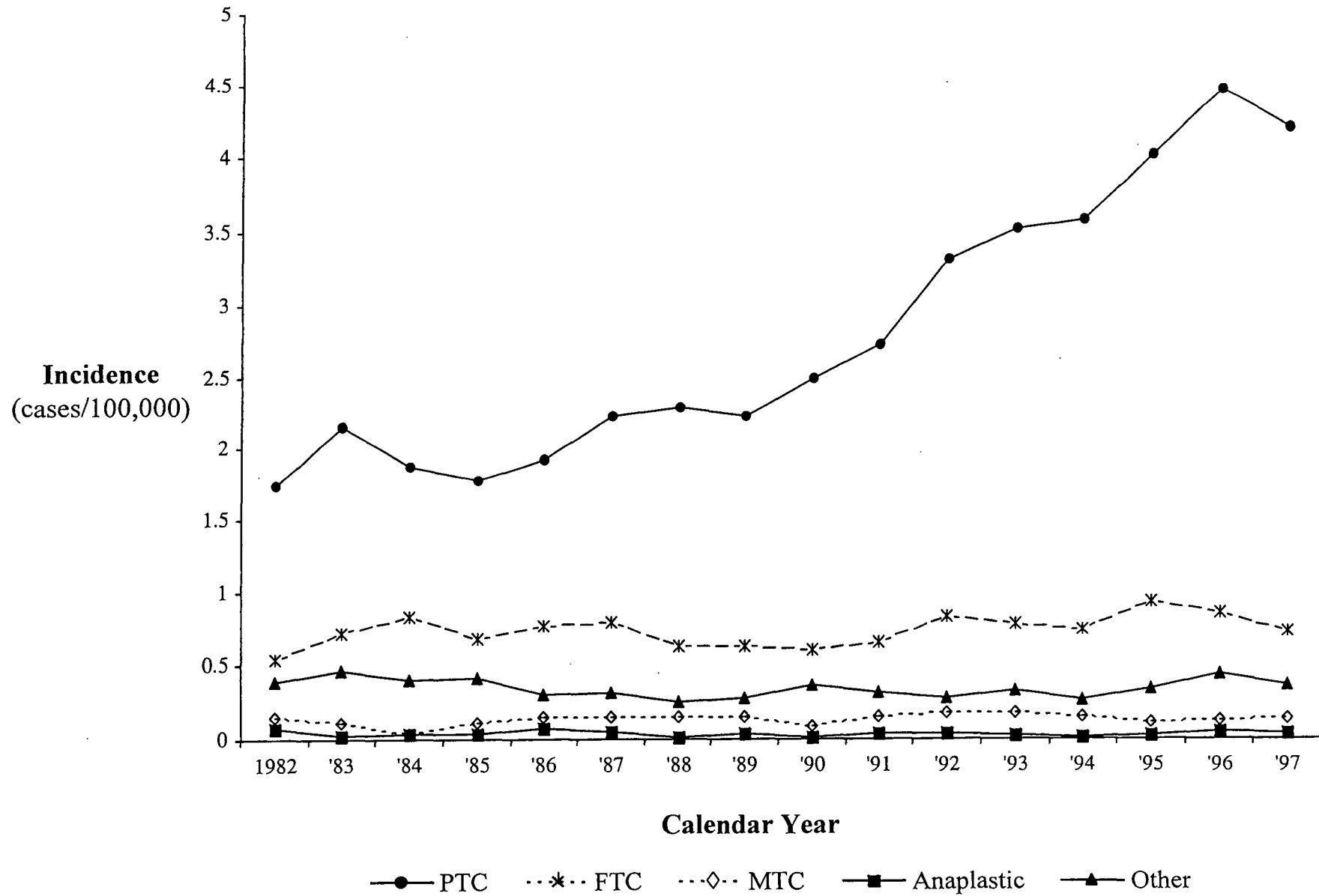


Figure 2.3 Thyroid carcinoma subtype incidence in Australia - males (1982 - 1997)

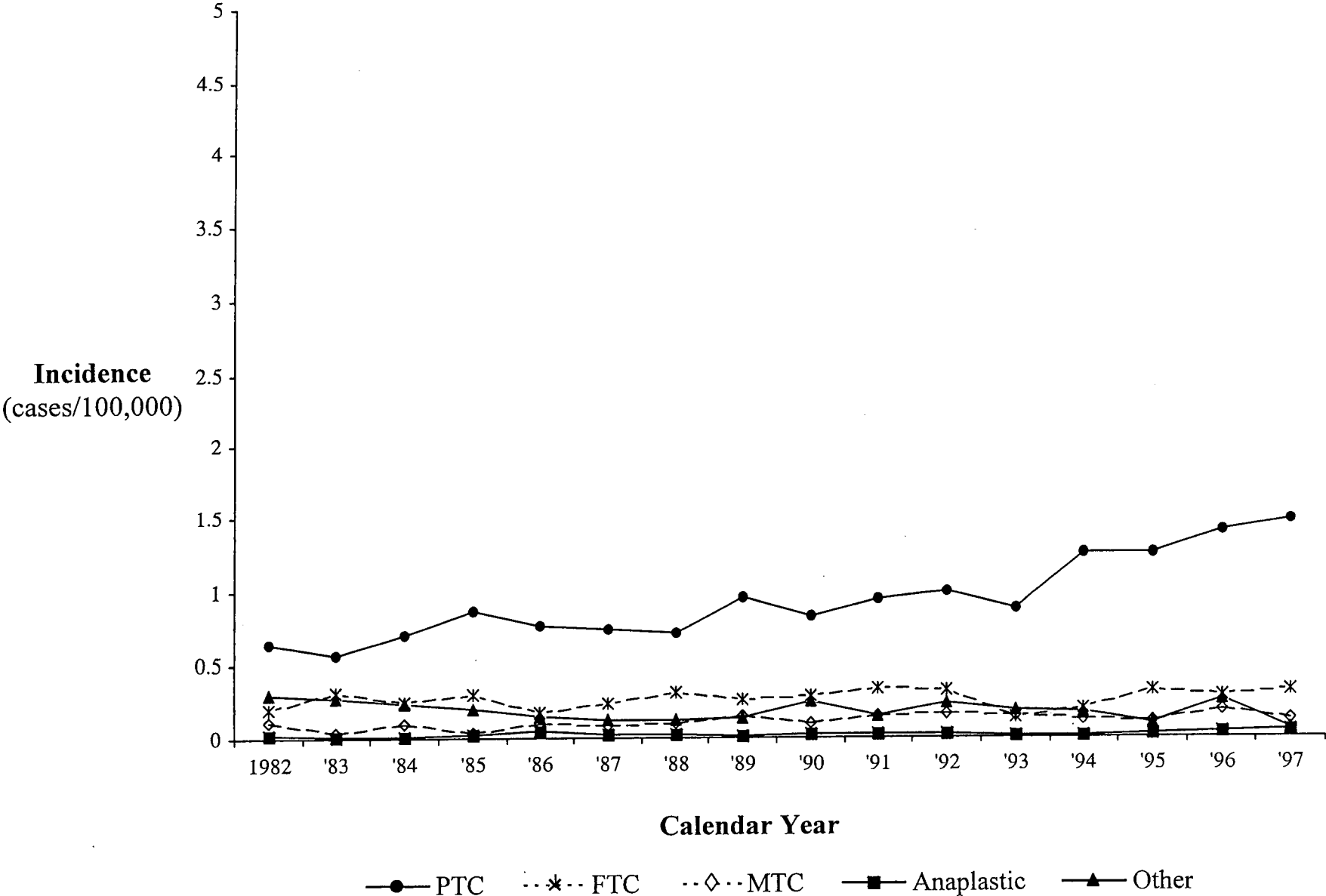


Figure 2.4 Papillary thyroid carcinoma subtype incidence in Australia - males & females (1982 - 1997)

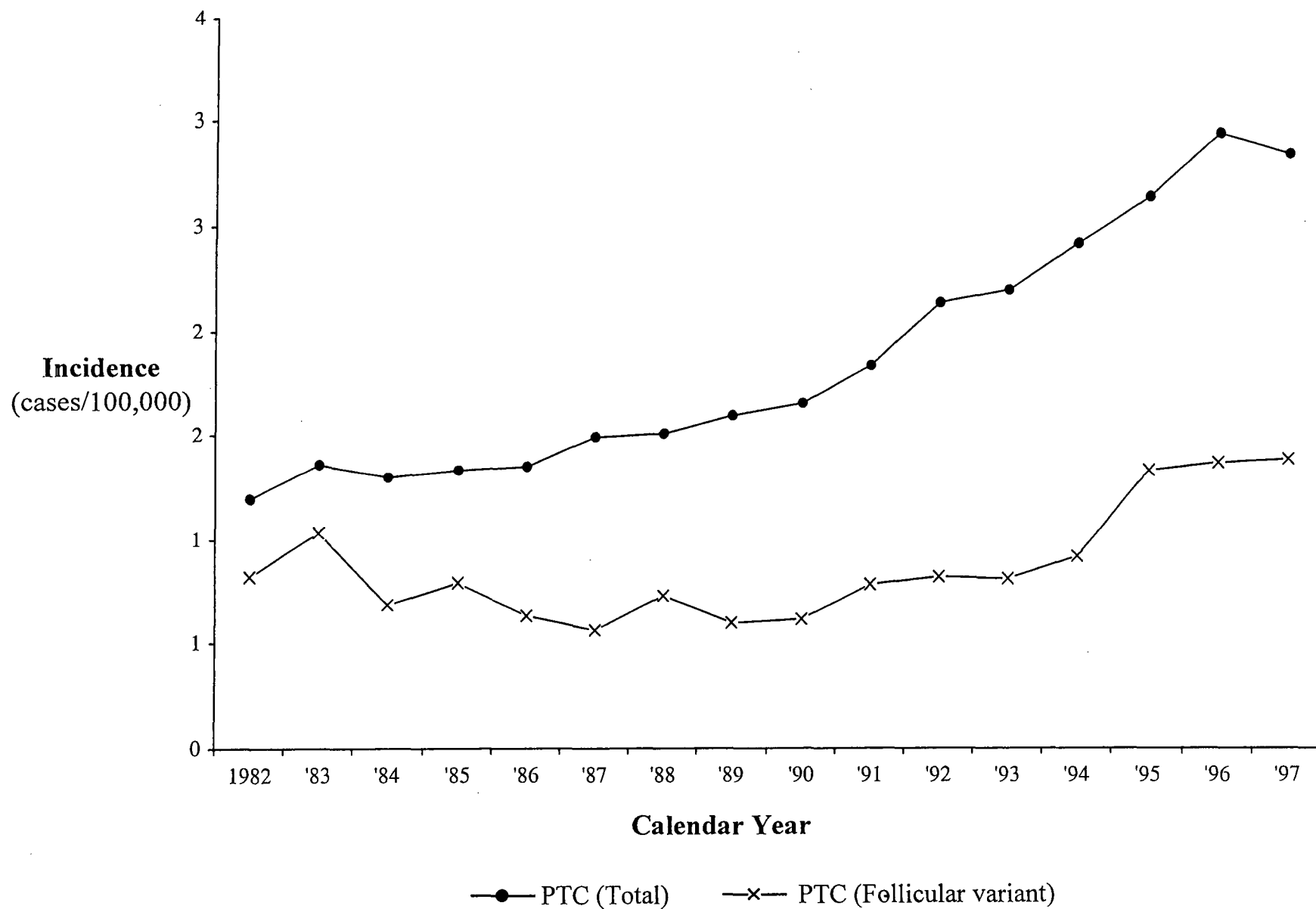


Figure 2.5 Average annual increase (%pa) in PTC (M+F) - relationship to geographic iodine status



CHAPTER 3

**A review of thyroid carcinoma cases registered by the
Tasmanian Cancer Registry (1978-1998) with particular
reference to the accuracy of case classification
and registration.**

Prologue

The key questions addressed by this chapter are:

- 1 Do changes in PTC classification or registration account for observed PTC incidence trends?
- 2 What contribution do small (≤ 1 cm) tumours make to PTC incidence trends?
- 3 Could historical variation in risk factors such as iodine nutrition explain observed PTC incidence trends?

Presentations and publications in relation to this Chapter:

Presented

This work was presented in part at the 42nd meeting of The Endocrine Society of Australia, Melbourne, Australia, 1999.

Published

Burgess JR, Dwyer T, McArdle K, Tucker P 2000 The changing incidence and spectrum of thyroid carcinoma in Tasmania (1978-1988) during a transition from iodine sufficiency to iodine deficiency. *J Clin Endocrinol Metab* 85: 1513-1517.

In accordance with the criteria for submission of thesis by previously published research, Chapter 3 is based on the above cited publication.

Aim

- 1 To assess the impact of changing histological diagnostic criteria on thyroid carcinoma incidence patterns.
- 2 To determine the relationship between PTC size and overall PTC incidence trends
- 3 To determine if evidence exists for a relationship between historical changes in iodine nutrition and PTC incidence trends.

Hypothesis

- 1 Changes in Cancer Registry case ascertainment and histopathological classification are unlikely to fully explain observed incidence trends for TC.
- 2 Increased diagnosis of small PTC accounts for the majority of the observed increase in PTC incidence.
- 3 Incidence trends for PTC are influenced by iodine nutrition.

Introduction

The previous chapter identified an increasing PTC incidence in Australia over the past two decades. Furthermore, a state-based geographic gradient for PTC incidence was identified in which the highest rate of increase was found in Tasmania. Tasmania is an island state of the Commonwealth of Australia and an area of endemic iodine deficiency(214, 215).

A number of distinct phases of iodine prophylaxis can be identified in Tasmania. Initially, potassium iodide tablets were provided to Tasmanian school age children between 1950 and 1965, whereas in 1966 iodine supplementation via the addition of potassium iodate to bread commenced(214, 215). Contemporaneous with this, iodine contamination of milk supplies by iodine residues (from a newly introduced dairy disinfectant) also provided an additional source of dietary iodine. Consequently, a well-documented transient increase in the incidence of iodine induced thyrotoxicosis occurred during the late 1960's and early 1970's(216).

In 1974, iodine supplementation of bread was discontinued and, thereafter, milk provided the primary method of community iodine repletion(214). For commercial reasons, the use of iodine containing dairy disinfectants declined in the late 1980s. During the period 1969–1981 only 4% of school children surveyed had urinary iodine to creatinine ratios less than 75 $\mu\text{g/g}$, whereas, during the years 1982–1985 the percentage below 75 $\mu\text{g/g}$ increased to 26%(214). Persistence of mild-moderate iodine deficiency has been confirmed by subsequent public health studies, including a 1996 analysis in which a

median urinary iodine excretion of 42 µg/L and in 2000 when median UIC was 84µg/L(217). More recently, studies have indicated the emergence of iodine deficiency in the other Australian states(19, 218, 219).

In this chapter, the incidence and spectrum of TC in Tasmania during the years 1978–1998 is evaluated with particular reference to the accuracy of Cancer Registry documentation and TC initial histopathological diagnosis. This period spans the transition of the Tasmanian population from iodine sufficiency to iodine deficiency.

Subjects and Methods

Data provided by the Australian Bureau of Statistics show that during the period 1978–1998 Tasmania's population increased by only 15% (62,000 persons) from a 1978 population of 413,538 persons. The male to female ratio remained stable during this period, ranging between 0.98 and 1.00. Inpatient medical services were provided by one tertiary referral hospital and eight smaller hospitals distributed throughout the island. By statutory regulation the Tasmanian Cancer Registry received notification of all cases of cancer (excluding non-melanoma skin cancer) diagnosed in the Tasmanian population.

Following approval by the Data Release Committee of the Tasmanian Cancer Registry, all cases of TC diagnosed during the period 1978–1998 were identified. A total of 298 cases of TC were registered in Tasmania between 1978 and 1998. Histopathological evaluation of tissue specimens has been undertaken by four pathology services. Review of the original histopathology reports and/or allied clinical details resulted in exclusion of nine (3%) cases that did not satisfy diagnostic criteria for a primary TC. The remaining 289 cases of primary TC were assigned to one of four diagnostic categories: PTC, FTC, MTC, and Other TC. To determine the comparability of diagnoses recorded by archival reports with contemporary diagnostic standards, original histology slides for all cases ($n = 134$) of PTC and FTC diagnosed during even numbered years commencing 1978 were sought for review by two histopathologists blinded to the original diagnosis.

Age standardized incidence rates were estimated using the world standard population age and gender weights(211). All incidence rates are per 100,000 of population. Data were analyzed using the Student's *t* test for normally distributed variables and the χ^2 test for nonparametric data. Where appropriate, numerical data is presented as mean \pm SEM.

Results

A total of 289 incident cases of TC were identified in Tasmania during the 21-year period spanning 1978–1998. PTC, FTC, MTC, and other TC accounted for 180 (62%), 67 (23%), 12 (4%), and 30 (11%) cases, respectively (*Table 3.1*). Of the 30 cases of other TC, 21 (70%) were classified as either anaplastic or undifferentiated thyroid cancer. The mean age at diagnosis was 50.8 ± 1.0 year, and the male to female ratio was 1:2.8 (*Table 3.1*). The median year for diagnosis was 1992. The age standardized incidence of TC (male and female) increased by 2.3-fold (from 0.75 to 1.76 per 100,000) and 2.2-fold (from 2.45 to 5.33 per 100,000), respectively, between 1978–1984 and 1992–1998 (*Figure 3.1*) ($P < 0.05$).

The overall increase in incidence for TC resulted predominantly from a rise in the incidence for PTC by 4.5- and 2.1-fold in females ($P < 0.05$) and males (not significant), respectively, between the periods 1978–1984 and 1992–1998 (*Figure 3.2*). The incidence of other categories of thyroid cancer did not change significantly (*Table 3.1*). During this time, the overall FTC/PTC ratio decreased from 0.74 to 0.24 ($P < 0.005$). The rise in incidence of PTC was observed in all Tasmanian population regions, spanning all pathology services. The rise in PTC incidence was, mostly, due to an increase in tumors of ≤ 1 cm in diameter; however, a 3-fold rise in incidence of larger lesions also occurred during the study period (*Table 3.2*).

Diagnoses of PTC were made at autopsy in eight (4%) cases. For non-PTC carcinoma, the presence of multinodular histopathology as a co-pathology in thyroid specimens remained stable during the study period (20% vs. 21%) between 1978–1984 and 1992–1998, respectively. During this time, the prevalence of multinodular change occurring in association with PTC increased from 11% to 36% ($P < 0.05$). Nine (5%) patients with PTC had an immediate familial history of PTC in which at least one first-degree relative was affected. This included two pairs of monozygotic twins with concordant development of PTC. Multifocal and metastatic PTC were identified in 43 (24%) and 33 (18%) patients, respectively (*Table 3.2*). Seventeen (40%) patients with multifocal PTC had bilateral tumours.

Histopathological material from 108 patients (diagnosed in the even numbered years) was available for prospective re-examination by two histopathologists blinded to original diagnoses. This sample represented 47% of all PTC and 34% of all FTC diagnosed during the entire time period from 1978–‘98. Diagnostic reclassification occurred for five (6%) PTC and four (17%) FTC (*Table 3.3*). Of the reclassified PTC’s, three were considered to be FTC and two were classified as papillary oncocytic neoplasms. Of the reclassified FTC, two were considered to be PTC and one each an adenoma and anaplastic carcinoma. Reclassifications did not alter the temporal trends observed at the *a priori* examination of original pathology reports.

Discussion

Consistent with the findings of Chapter 2, there was a significant rise in the incidence of TC during the study period. This resulted from an increase in incidence of small PTC. Changes in clinical practice, such as fine sectioning of thyroidectomy specimens resected for benign indications (such as multinodular goitre, increased use of ultrasonography and FNAB) may account for this. However, such factors are unlikely to fully explain the observed trends. By way of example, despite a rise during recent years of multinodular goiter occurring in association with PTC, the majority of patients with combined PTC and multinodular goiter had evidence of clinically relevant malignancy. Of the 39 cases of PTC associated with multinodular goiter diagnosed during the 1992–1998 period, in 8 (21%) cases the PTC was more than 3 cm in diameter, in 11 (33%) cases it was multifocal, and in 2 (6%) cases it was metastatic. Furthermore, even when lesions of 1 cm or less in diameter are excluded, a 3-fold rise in the incidence of larger PTC was evident (*Table 3.2*).

The role of iodine nutrition in the pathogenesis of TC is both complex and controversial(29, 103, 161, 162, 220). Comparison of incidence rates between iodine-deficient and iodine-sufficient communities yields conflicting results(95, 162). Similarly, case control studies have also produced contradictory findings, iodine-rich diets having been associated with both a heightened and an attenuated risk of TC(221-223). Despite this, a relatively consistent association has been the link between iodine nutrition and tumor histology(27, 161, 162). The incidence of FTC and anaplastic TC is greatest in iodine-deficient populations, whereas the converse is true in regions of iodine

sufficiency(29, 161, 163, 220). Consistent with this observation, iodine supplementation in previously deficient populations is associated with a rise in the proportion of PTC; so called "papillarization" of TC(28, 29, 161, 163, 220). This is evidenced by a rise in the proportion PTC relative to FTC(163, 166).

Few studies of iodine nutrition had been undertaken on the Australian mainland prior to the recent National Iodine Nutrition Study (NINS) (218). Before the 1970's several localised areas with endemic goitre were recognised on the Australian east coast(17, 19, 214, 224). Agricultural studies of ovine iodine nutrition and thyroid function indicate iodine deficiency in grazing sheep in Tasmania, Victoria, NSW and southern QLD(17, 225). Similarly, the river systems of Australia's east coast have been shown to be iodine deplete(17, 224). The recent NINS confirmed a similar distribution of iodine deficiency in the contemporary human population of Australia(218).

It is likely that iodine nutrition across much of Australia was rendered adequate unwittingly from the mid 1960's until the late 1980's by use of iodine based disinfectants (iodophors) in the Australian dairy industry, the residue of which enhanced milk iodine content(214). However, declining use of iodophor disinfectants over the past two decades appears to have unmasked underlying Australian regional variations in the ecological distribution of iodine deficiency(19, 218, 219).

It is therefore notable that in Tasmania, the increase in PTC incidence described in this chapter has occurred despite the recurrence of iodine deficiency. A complex interaction between iodine nutrition and thyroid tumorigenesis may account for this. A study by

Galanti *et al.* indicated a possible differential effect for iodine prophylaxis on the spectrum of TC depending on an individual's age at the time of iodine exposure (27). The increasing incidence and predominance of PTC despite the fall in contemporary iodine nutrition could also reflect either a threshold for changes in iodine nutrition or a latency between changes in iodine intake and the clinical expression of neoplastic disease.

It is also possible the current rise in PTC incidence relates to a delayed impact of the relative iodine excess occurring during the late 1960s and early 1970s (214, 215). Whereas this was associated with an acute increase in the incidence of thyrotoxicosis at the time, it may also have primed susceptible individuals, then in their childhood, for subsequent development of PTC as adults (214, 216). If this speculation is correct, a fall in the incidence of PTC might be expected over the following decade.

Ionising radiation is the external aetiological factor most clearly associated with an heightened risk of clinically significant TC(136, 137, 206). Nuclear fallout (radioiodine) and medical sources of ionising radiation confer an increased risk of both benign and malignant nodular thyroid disease(134, 136, 137, 139, 144). Exposure to ionising radiation during childhood increases the likelihood of PTC developing in adult life(133, 137, 138, 209). Tumours occurring in this context are often multicentric and may develop after a latency of several decades(133, 136, 137, 226). Moreover, PTC rates may not reach a maximum until 30 years following the exposure(133, 136, 137, 226).

Exposure to radioiodine fallout from nuclear weapon testing is a possible link between the distribution of ID in Australia and geographic patterns of PTC incidence(134, 226).

Atmospheric nuclear weapon testing occurred both in Australia and elsewhere in the South Pacific between 1950 and 1962 (227). The highest predicted susceptibility to PTC from fallout related to this maps to birth years 1945–1962. Children born during this period were exposed potentially to fallout at a time when community iodine nutrition was suboptimal, enhancing the risk of thyroidal exposure to ionizing radiation(134, 214).

Medical use of ionizing radiation in childhood is also associated with an heightened risk for PTC in adulthood(135). External beam radiotherapy was employed in the mid-twentieth century for treatment of a diverse range of non-neoplastic conditions (135). The prevalence of such therapy in Australia is unclear and warrants further consideration as an etiological risk factor in the context of current PTC incidence trends.

Conclusions

The increased incidence of PTC observed by Cancer Registries throughout Australia in Chapter 2 has been confirmed by detailed review of source documentation for cases registered by the Tasmanian Cancer Registry. An increase in small ($\leq 1\text{cm}$) PTC is the major component of the observed change, although a minor increase in the incidence of large and aggressive PTC has also occurred. Potential explanations for this include both changes in clinical and diagnostic practice as well a rise in underlying thyroid tumorigenesis driven by factors associated with changes in iodine nutrition or exposure to ionising radiation. A more detailed review of clinical practice trends and risk factor exposure is required to further assess these possibilities.

**Table 3.1 Characteristics of thyroid carcinoma diagnosed during the calendar
years 1978-1998**

Year of Diagnosis	Papillary	Follicular	Medullary	Other
1978 – 1984				
n (% total TC)	27 (47)	20 (35)	2 (4)	8 (14)
Crude Rate	0.90	0.67	0.06	0.26
Age	46.8±2.9	57.8±3.6	42.5±21.0	71.8±3.9
M:F	1 : 2	1 : 5.7	0 : 2	1 : 1.7
1985 - 1991				
n (% total TC)	43 (54)	21 (26)	3 (4)	13 (16)
Crude Rate	1.36	0.66	0.09	0.41
Age	47.6±2.5	49.4±3.6	50.4±8.8	65.6±4.9
M:F	1 : 3.3	1 : 3.2	1 : 2	1 : 1.6
1992 - 1998				
n (% total TC)	110 (72)	26 (17)	7 (5)	9 (6)
Crude Rate	3.32	0.78	0.06	0.27
Age	45.9±1.3	54.7±2.3	57.2±5.8	70.9±5.7
M:F	1 : 4.2	1 : 1.4	1 : 0.8	1 : 0.8

M:F – Male : Female ratio

Crude rate – Crude incidence rate per 100 000 of population

Table 3.2 Changes in the spectrum of papillary thyroid carcinoma diagnosed during the periods 1978-1984, 1985-1991 and 1992-1998

Characteristic	1978 - 1984**		1985 - 1991		1992 - 1998**	
	<i>n (%)</i>	<i>M:F</i>	<i>n (%)</i>	<i>M:F</i>	<i>n (%)</i>	<i>M:F</i>
Total cases	27	1 : 2	43	1 :3.3	110	1:4.2
Size <1.1	7 (26)	1 : 2.5	12 (28)	1 : 5.0	49 (45)	1 : 5.1
Size 1.1-2.0	8 (30)	1 : 1.7	15 (35)	1 : 4.0	33 (30)	1 : 4.5
Size 2.1-3.0	5 (19)	1 : 1.5	9 (21)	1 : 3.5	13 (12)	1 : 5.5
Size >3.0	5 (19)	1 : 1.5	7 (16)	1 : 1.3	13 (12)	1 : 2.3
Multinodular pathology	3 (11)	1 : 0.5	12 (28)	1 : 5.0	39* (36)	1 : 3.9
Incidental finding	3 (11)	1 : 2.0	9 (21)	1 : 8.0	33 (30)	1 : 6.0
Multifocal primary	1 (4)	0 : 1.0	11 (26)	1 : 4.5	31 (28)	1 : 2.9
Regional invasion	3 (11)	1 : 2.0	7 (16)	0 : 7.0	12 (11)	0 : 12
Metastases	7 (26)	1 : 0.4	10 (23)	1 : 9.0	16 (15)	1 : 1.3
Deceased	6 (22)	1 : 1	8 (19)	1 : 1.7	6 (6)	1 : 1

M:F – Male : Female ratio

Size – Tumour size

Multinodular pathology – Histopathological evidence of multinodular change in thyroid tissue.

**Size unknown in 2 cases of papillary carcinoma.

*Of these 39 cases of thyroid carcinoma, 8 were >3cm in diameter, 11 were multifocal, 2 were metastatic, and 16 were incidental findings.

**Table 3.3 Comparison of original and contemporary histopathological diagnoses
for 108 cases of differentiated thyroid carcinoma.**

	1978 - 1984		1985 - 1991		1992 - 1998	
	<i>n</i> =	%	<i>n</i> =	%	<i>n</i> =	%
<i>Original diagnosis- PTC</i>	18		20		62	
Cases available for review*	15	83	16	80	54	87
- PTC confirmed**	13	87	15	94	52	96
<i>Original diagnosis- FTC</i>	10		10		14	
Cases available for review*	6	60	5	50	12	86
- FTC confirmed**	4	67	5	100	10	83

Original diagnosis - Diagnosis as recorded on the original histopathology report.

*Histopathology slides were located and reviewed by pathologist. Percentage represents the proportion of patients for whom slides were located.

**Re-examination of histopathology produced a diagnosis concordant with original diagnosis. Percentage represents the proportion of patients for whom the review diagnosis was concordant with the original diagnosis.

Figure 3.1 Age standardised incidence rate of thyroid cancer in Tasmania 1978 - 1998

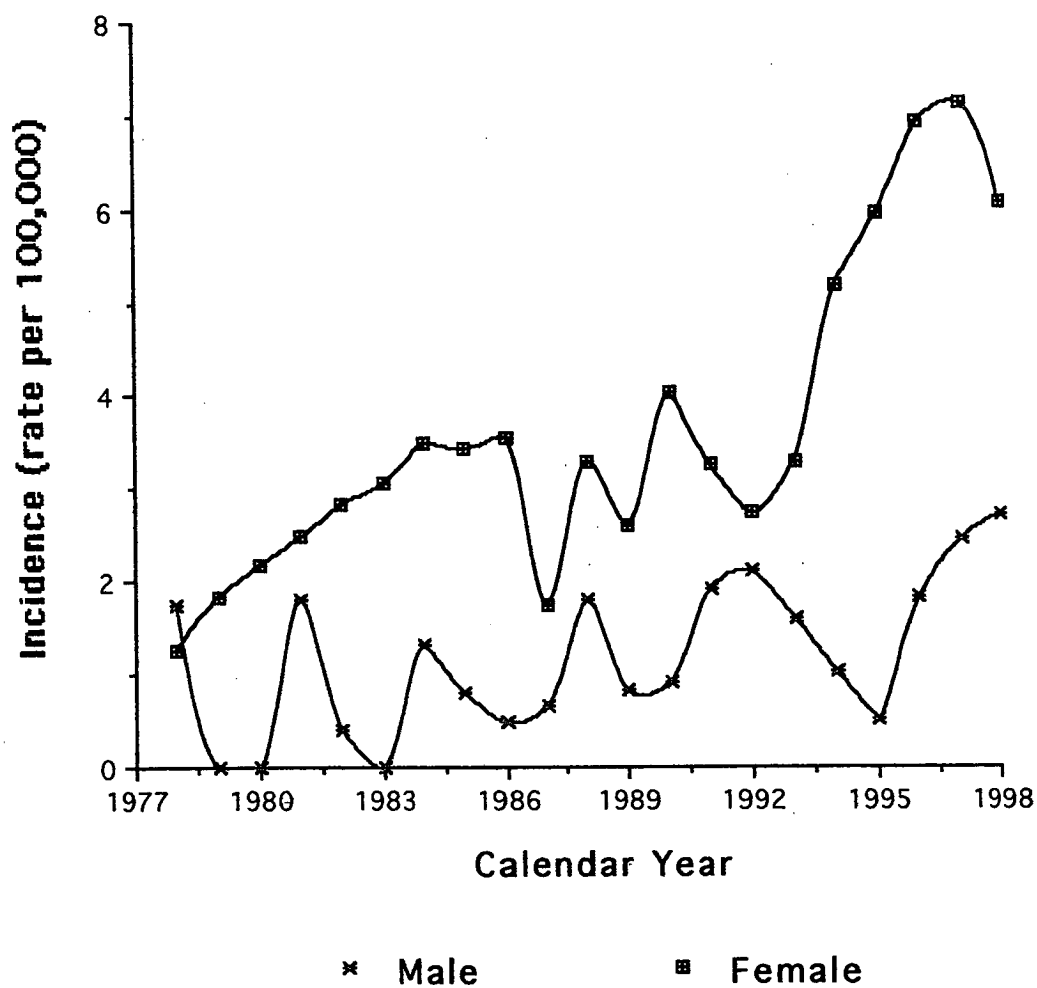


Figure 3.2 Thyroid cancer histology and year at diagnosis

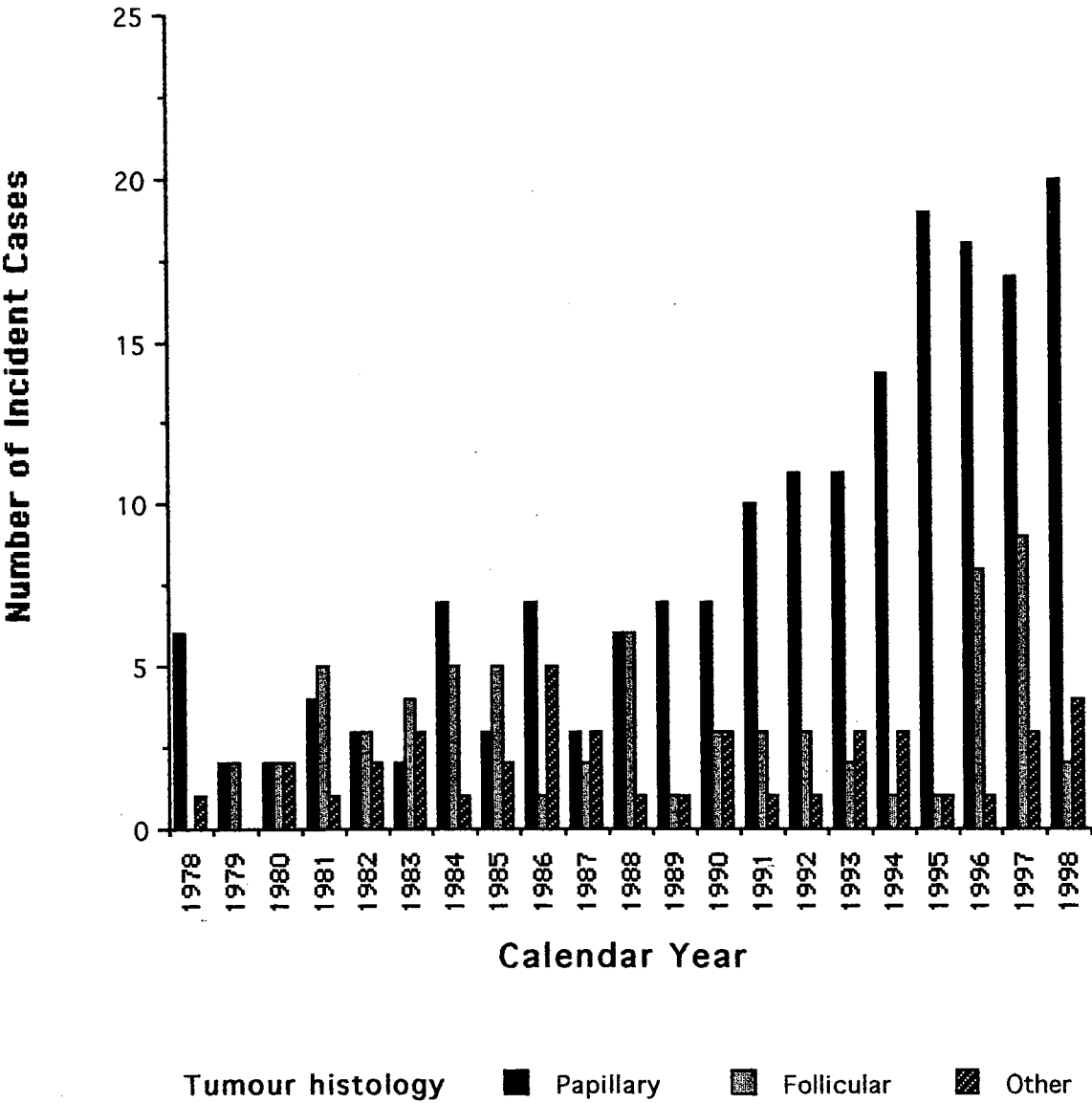


Figure 3.3 Sex distribution for incident cases of PTC

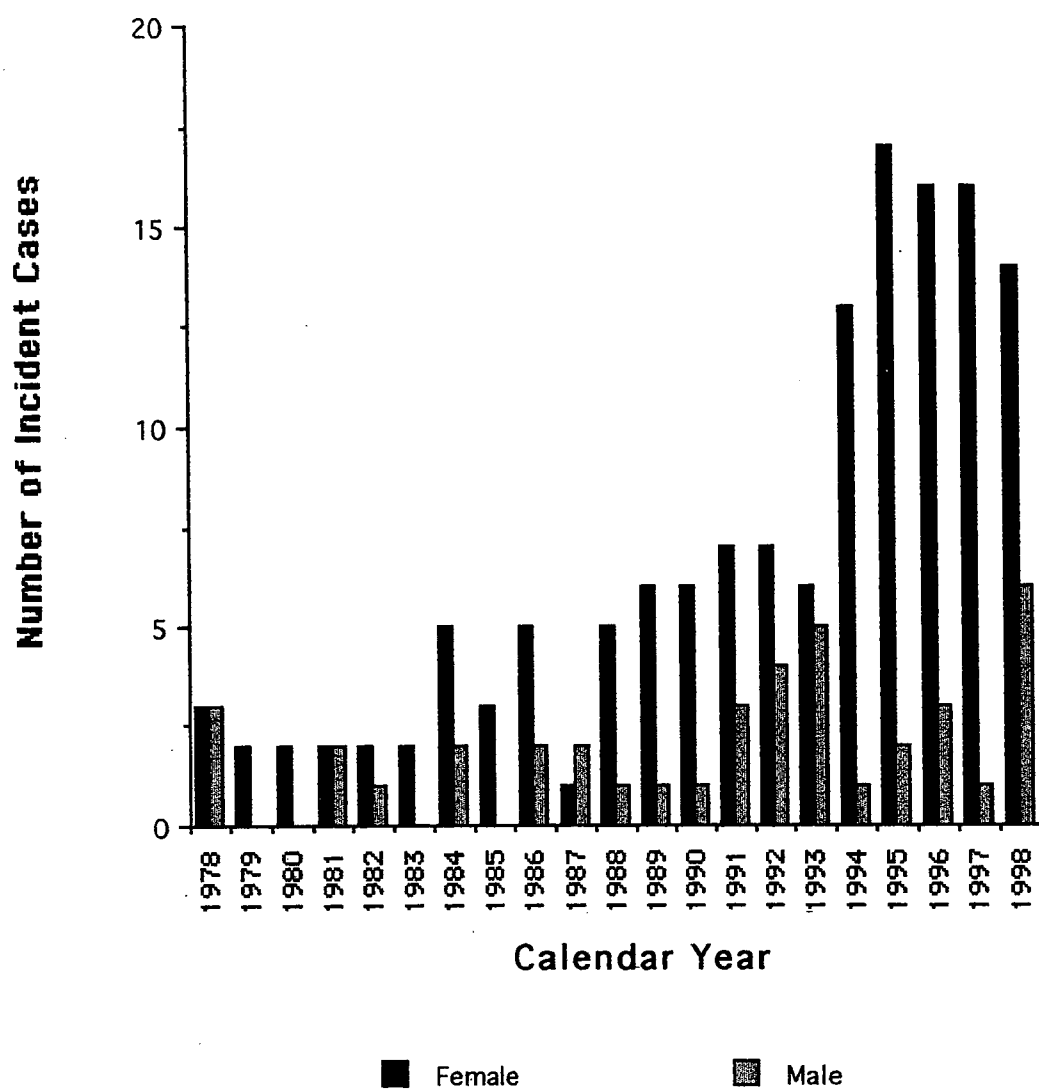
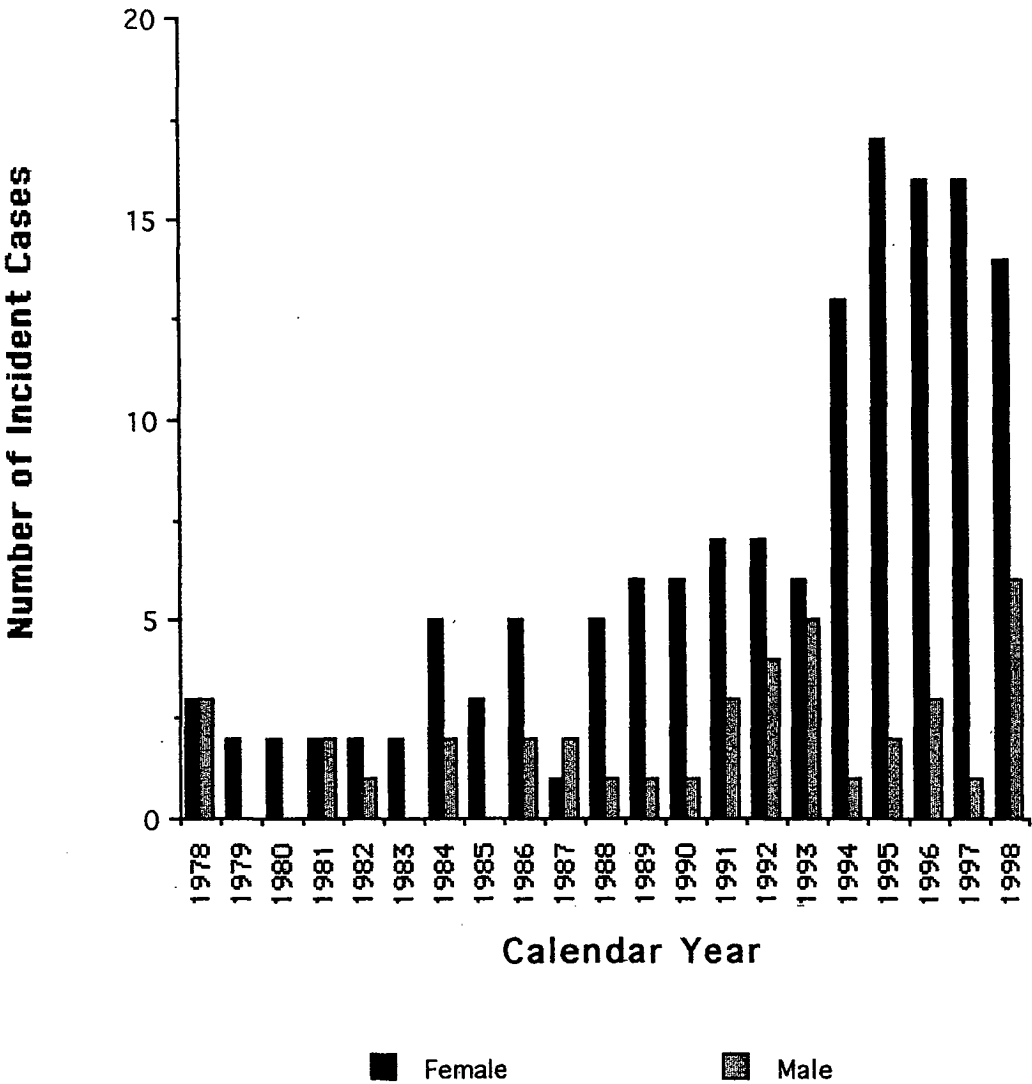


Figure 3.3 Sex distribution for incident cases of PTC



CHAPTER 4

**Incidence trends for PTC and their correlation with trends for
thyroid surgery and thyroid FNAB cytology**

Prologue

The key questions addressed in this Chapter are:

- 1 What is the completeness of Tasmanian Cancer Registry case ascertainment for diagnoses of PTC?
- 2 Has there been a change in patterns for utilization of FNAB and thyroid surgery?
- 3 Is there a relationship between thyroid imaging, FNAB and PTC incidence trends?

Presentations and publications arising from this Chapter:

Presented

Preliminary results presented at the Endocrine Society of Australia, 2002 ASM, Adelaide, Australia.

Published

Burgess JR, Tucker P. 2006 Incidence trends for papillary thyroid carcinoma and their correlation with thyroid surgery and thyroid fine needle aspirate cytology. *Thyroid* 2006; 16: 47-53.

In accordance with the criteria for submission of thesis by previously published research, Chapter 4 is based on the above cited publication.

Aim

- 1 To confirm the adequacy PTC case ascertainment by the Tasmanian Cancer Registry.
- 2 To determine the relationship between thyroid surgical and cytological procedures and temporal trends for PTC diagnosis.

Hypothesis

Incidence trends for PTC are influenced by changing paradigms for evaluation and management of nodular thyroid disease.

Introduction

Previous chapters demonstrated an increase in incidence of PTC in Australia generally, and Tasmania in particular(213, 228). Detailed review of source documentation and tissue samples for cases registered by the Tasmanian Cancer Registry confirmed both the accuracy of case registration as well as the consistency of histopathological classification over time. However, the potential for changes in TC case notifications over time could not be assessed by the methodology utilized in previous chapters. Progressive and systematic improvements in Cancer Registry case ascertainment is potentially an important source of bias.

Prior chapters have also linked the ecological distribution of iodine deficiency in Australia with PTC incidence trends(17, 218, 228). As iodine deficiency is often associated with goitre monitoring programs, it is possible increased screening accounts for the majority of observed changes in PTC incidence(71, 200, 229, 230). In support of this I have previously identified an increase in the incidence of tumours $\leq 1.0\text{cm}$, lesions which most likely represent asymptomatic and non-palpable PTC (occult PTC) (71, 170, 228, 230). Such PTC generally have a “biologically benign” natural history (41, 71, 202, 205). It is therefore possible that identification of non-palpable nodules by ultrasonography, and their subsequent cytological evaluation by FNAB, has merely increased the diagnosis of small and mostly clinically inconsequential tumours (41, 202, 212, 230). At present however, there is a paucity of data directly relating trends for PTC incidence to trends in the use of neck ultrasonography, thyroid FNAB cytology and thyroid surgery (230). Such information would assist in determining the role, if any

contemporary medical practice has had on PTC incidence trends.

Using the Tasmanian population as a model, this study sought to determine the relationship between changes in PTC incidence and trends for utilization of neck ultrasonography, thyroid surgery and thyroid FNAB cytology over an 11-year period during which PTC incidence increased more than two fold(213).

Subjects and Methods

Hospital and pathology services in Tasmania submitted data relating to thyroid surgical, histopathological and cytological procedures undertaken between January 1988 and December 1998. This period was selected given the availability of comprehensive data relating to surgical procedures and pathology outcomes, in conjunction with the availability of accurate baseline cancer registry data for thyroid carcinoma (213). Furthermore, during this period Tasmania's population increased by less than 15% (213). In subsequent years population flux increased and data availability diminished.

Data was cross-referenced against diagnoses of thyroid carcinoma independently assembled by the Tasmanian Cancer Registry - a statutory authority that receives notification of all cases of cancer (excluding non-melanoma skin cancer) diagnosed in the Tasmanian population (213). All tumours designated as primary thyroid carcinoma were assigned to one of four diagnostic categories; PTC, FTC, MTC, and "Other diagnoses" (213, 228). The category of "Other diagnoses" comprised anaplastic thyroid carcinoma, Hurthle cell malignancy and "carcinoma not otherwise specified". Cytology results from FNAB thyroid were classified into four categories; *unsatisfactory sample* (U), *benign lesion* (B), *indeterminate lesion* (I) and *malignant* (M). The *indeterminate* category comprised follicular lesions, oncocytic lesions, and other indeterminate or suspicious cytological appearances.

In addition, patients identified by the Tasmanian Cancer Registry with a diagnosis of PTC during the period 1978-1998 (n=180, Female:Male=3.5, Age at diagnosis 46.4 ± 1.1 years) were also sought to determine the preoperative likelihood of TC. Of these, 99 patients (Female:Male=4.8, Age at diagnosis 44.5 ± 1.0 years) were living, contactable and consented to provide information regarding the original indication for thyroid surgery.

Normally distributed variables were analysed using the Student's t-test. Time trends in incidence were analysed by linear regression of the rates on year at diagnosis. Numerical data is presented as Mean \pm Standard Error of Mean (SEM). Age standardised incidence rates (ASR) were estimated using the World Standard Population age and gender weights, and are expressed per 100 000 of population (211). The study was approved by the Royal Hobart Hospital Research Ethics Committee and the Data Release Committee of the Tasmanian Cancer Registry.

Results

In the years 1988-1998 a total of 3452 individuals underwent a thyroid procedure, comprising 1968 surgical procedures in 1920 patients (F:M 4.5:1) and 1756 FNAB cytological procedures in 1532 patients (F:M 5.3:1). A new diagnosis of TC was made in 184 patients with a female to male ratio of 3:1. Of these, 175 patients had an histologically confirmed diagnosis - 121 (65.8%) PTC, 40 (21.7%) FTC, 7 (3.8%) MTC and 17 (9.2%) "Other diagnoses. When PTC cases registered by the Tasmanian Cancer Registry were compared with the results of the current study, only 13 previously unrecognised cases of PTC were identified, indicating Registry ascertainment for the period 1988-1998 was 93.9% complete (*Figure 4.1*).

Forty patients with a malignant diagnosis underwent an initial subtotal thyroidectomy followed by completion thyroidectomy once malignancy was identified. Nine (4.9%) cases were diagnosed by FNAB cytology alone, without histopathological material being available for subsequent evaluation. Of 175 patients with an histopathological diagnosis of TC, 70 (40%) had at least one preoperative assessment using FNAB cytology (14 benign cytology, 42 indeterminate, 12 malignant, 7 unsatisfactory and one result unavailable for review). Of the 42 patients with indeterminate cytological results - follicular lesions accounted for 24, oncocytic lesions 4, and other atypical appearances were reported in 14 cases.

During the study period the age standardized rate for thyroidectomy increased by 6.8% per year for females and 10.9% per year for males ($p < 0.05$) (*Table 4.1, Figure 4.2*). Similarly, FNAB usage increased at a rate of 66.2% per year for females and 17.6% per year for males ($p < 0.005$) (*Table 4.1, Figure 4.2*). During this time the median age at thyroidectomy and FNAB remained stable at 48 years and 49 years respectively. There was an 147.6% per year increase in the use of preoperative FNAB prior to thyroidectomy ($p < 0.001$) and no significant increase in thyroidectomy without prior FNAB (0.1% per year increase, $p = 0.24$) (*Table 4.1*). In the latter part of the study period preoperative FNAB exhibited less restriction to lesions ultimately found to be malignant than was the case initially (*Table 4.2, 4.3*).

The likelihood of diagnosing a PTC in any given thyroidectomy specimen increased from 3.3% in 1988 to 7.7% in 1998 (*Table 4.2*). Diagnoses of PTC in patients previously assessed by FNAB increased by 99.7% per year ($p < 0.005$), whilst for those in whom a prior FNAB was not performed the increase was 10.1% per year ($p < 0.05$). The increase in PTC for patients assessed by FNAB was evident for tumours ≤ 1 cm as well as those > 1 cm diameter – although the increase was greater in the former (*Table 1*). Although not reaching statistical significance, there was also a trend (10.1% per annum) for increase in PTC > 1 cm without history of pre-operative FNAB evaluation (*Table 4.1*).

To evaluate prevalence trends for incidental diagnoses of PTC, all patients identified by the Tasmanian Cancer Registry with PTC during the period 1978-1998 were sought for completion of a questionnaire regarding the preoperative likelihood of malignancy. There was a 63.6% increase in the diagnoses of PTC ≤ 1 cm diameter in individuals with a

low preoperative likelihood of malignancy, and this accounted for the majority of increased PTC diagnoses between the time periods 1978-'91 and 1992-'98 (*Table 4.4*).

Discussion

This study suggests an increase in the diagnosis of small PTC resulting from contemporary clinical practices (increased neck imaging and FNAB) is likely to account for the majority of the observed increase in PTC incidence (71, 230). Improvements to Cancer Registry case ascertainment does not account for the rise in PTC incidence. Whilst it is unlikely my methodology captured every eligible thyroid procedure, this study does provide a robust estimate of total thyroid surgical and cytological procedures performed in the Tasmanian population during the study period. Over this time, only thirteen cases of thyroid carcinoma not originally registered by the Tasmanian Cancer Registry were identified (*Figure 4.1*). Similarly, a previous review of tumours recorded by the Tasmanian Cancer Registry (presented in Chapter 3), determined that incorrect histological classification either at the Registry, or at the time of original histological diagnosis, occurred in less than 10% of cases (213). Thus, there is no suggestion that procedural changes in relation to Cancer Registry case ascertainment have resulted in observed PTC incidence trends.

Thyroidectomy and FNAB cytology rates have increased by 7% per year and 49.7% per year respectively in Tasmania (*Table 4.1*). As evidenced by the increased use of FNAB in patients ultimately diagnosed with benign lesions and small PTC, there appears to have been a trend towards decreased restriction of pre-operative FNAB to patients at high *a priori* cancer risk (*Table 4.2*). Particularly in the later years of the study period, not only was cytology used more frequently, it was more likely to be used less selectively - preoperative cytological findings and final histology were less concordant.

Broader use of FNAB is further suggested by the increasing proportion of patients undergoing pre-operative FNAB cytology for whom the ultimate diagnosis was a benign lesion (*Table 4.2, 4.3*). It appears FNAB was initially reserved for “high” risk patients, but in more recent years FNAB seems to have been offered more generally to “lower” risk individuals. This is in keeping with promotion and acceptance of an evaluation protocol for thyroid nodules that recommends FNAB for the majority of thyroid nodules found in patients with a non-suppressed TSH (71, 75, 76, 212).

Whilst it is not possible to directly quantify the effect of increased use of neck imaging (CT and ultrasonography) on the identification of “occult” PTC, there has been a substantial rise in the use of neck imaging since the early 1980’s. Neck ultrasonography in particular appears to have become widely used in primary medical practice for the evaluation of non-specific neck symptoms and vascular conditions, as well as for clinically evident thyroid indications. Australian government data show the number of neck ultrasound procedures performed in Tasmania increased markedly between 1993 – 1998 (*Figure 4.3*).

In the context of increased use of medical imaging and contemporary medico-legal sensitivities it is not surprising that current trends are seen. Impalpable and asymptomatic thyroid nodules are a common finding when the thyroid is imaged for non-nodular indications or evaluated at autopsy. The prevalence of PTC diagnosed antemortem is approximately 0.1%, versus up to 13% for occult PTC in autopsy series (170, 202, 205). Whilst most nodules identified by neck imaging are benign (colloid nodules and follicular adenomas), an important minority are PTC, the majority which are

≤1cm in diameter. Therefore increased use of neck ultrasound imaging in conjunction with consequential FNAB cytological evaluation could account for much of the observed increase in diagnoses of PTC ≤1cm diameter (201, 205, 210, 228, 230).

Most studies of the natural history of such lesions have concluded these “occult” PTC mostly follow an indolent course and have an excellent prognosis (83, 182). However a proportion of incidental thyroid carcinoma are destined to become a clinically relevant. The study by Nam-Goong *et al* showed that a proportion of incidental identified PTC were associated with extrathyroidal extension or metastases (83). At present however, there is no reliable way of selecting for excision those lesions destined to produce clinically relevant malignancy, whilst sparing the majority of patients with indolent disease from an unnecessary thyroidectomy. The standard of care therefore remains resection of thyroid “incidentalomas” if initial cytology is suspicious for malignancy.

The possibility of a true biological change affecting the incidence of PTC cannot be fully excluded by this study. The trend for increased incidence of larger (>1cm) PTC, suggests that improved recognition of “occult” PTC may not account for all of the observed incidence increase (*Table 4.3*). In particular, the incidence of PTC >1cm in patients for whom a preoperative FNAB had not been undertaken, has also increased by 10.1% annually. Whilst a proportion of these tumours may have been clinically “occult”, it is likely many were symptomatic or clinically palpable at presentation. This is supported by the findings presented in *Table 4.4*.

Therefore, a complex mix of underlying processes is likely to have resulted in the change to PTC incidence observed during the latter part of the 20th century (60, 139, 163, 170, 202, 206). The current study suggests the increased PTC incidence is mostly due to

identification of “occult” PTC (greater use of ultrasonography and FNAB cytology, lower thresholds for thyroidectomy and heightened scrutiny during histopathological assessment). In addition a smaller but real increase in underlying PTC incidence may also have occurred.

Conclusions

Over the past two decades there has been a substantial increase in the use of neck ultrasonography and consequently thyroid FNAB cytology to evaluate small and otherwise asymptomatic thyroid nodules. Thyroidectomy rates appear to have risen in response to increased use of FNAB and the consequential increase in reporting of suspicious cytology. However, the rise in incidence of PTC >1cm diameter suggests that a true increase in PTC incidence rates has also occurred. Given parallels between the overall change in PTC incidence observed in Tasmania as well as other parts of Australia as well as globally, the findings of the current study are likely to be of value in understanding the world-wide rise in PTC incidence observed in recent decades.

Additional studies are also required to evaluate the role of established risk factors (such as ionising radiation and genetic susceptibility), as well as further elucidating the role of iodine nutrition in trends for PTC.

Table 4.1 Statistical characteristics of thyroid procedures undertaken and PTC diagnosed in Tasmania (1988-1998)

Subgroup	Average Annual increase (%)	Confidence Interval		R ²	P =
		Lower 95%	Upper 95%		
Thyroidectomy (M+F)	7.0	4.1	9.9	0.77	<0.001
Female	6.8	4.2	9.4	0.80	<0.001
Male	10.9	1.8	20.0	0.45	0.024
Thyroid FNAB (M+F)	49.7	37.7	61.7	0.91	<0.001
Female	66.2	48.6	83.9	0.89	<0.001
Male	17.6	8.9	26.2	0.70	0.001
Thyroidectomy (M+F) (FNAB)*	147.6	107.9	187.3	0.89	<0.001
Thyroidectomy (M+F) (no FNAB)	0.1	-0.8	2.9	0.15	0.239
Diagnosis of PTC (M+F) ⁺					
Prior FNAB (M+F)**	99.7	39.4	160.1	0.78	0.005
Size ≤1 cm (M+F) ⁺⁺	>100%	na	na	na	na
Size >1 cm (M+F)	63.9	9.3	118.5	0.44	0.027
No Prior FNAB	10.1	2.5	17.6	0.71	0.014
Size ≤1 cm (M+F)	10.0	-14.7	34.6	0.24	0.385
Size >1 cm (M+F)	10.1	-0.5	25.8	0.44	0.177

*Patients undergoing thyroidectomy (partial or total) following a prior FNAB

⁺ New (incident) cases of PTC diagnosed at histology following thyroid surgery

** New (incident) PTC diagnosed after thyroid surgery in patients for whom an FNAB has previously been performed.

⁺⁺ No cases identified for the initial six years of study – exact percentage change per annum unable to be calculated

Table 4.2 **Time trends for thyroid histology and their relationship to preoperative FNAB cytology**

Histology Outcome	FNAB status prior to Thyroidectomy					
	1988 - 1992			1994 - 1998		
	<i>Total</i>	<i>No FNAB</i>	<i>FNAB</i>	<i>Total</i>	<i>No FNAB</i>	<i>FNAB</i>
Histology - benign						
Number of cases	645	609	36	961	688	273
Proportion of cases (%)	92.3	94.0	70.6	89.5	92.2	83.2
Female :Male ratio	4.5	4.5	4.1	4.7	4.1	7.5
Median age (y)	50	50	48	49	49	49
Histology - PTC						
Number of cases	33	27	6	82	45	37
Proportion of cases (%)	4.7	4.2	11.8	7.6	6.0	11.3
Female :Male ratio	4.5	5.8	2	6.5	8.0	5.2
Median age (y)	45	49	42	44	44	44
Histology - Other TC						
Number of cases	21	12	9	31	13	18
Proportion of cases (%)	3.0	1.9	17.7	2.9	1.7	5.5
Female :Male ratio	1.3	1.4	1.3	1.2	0.9	1.6
Median age (y)	45	48	41	56	74	52

Table 4.3 **Time trends for thyroid histology and their relationship to pre-operative cytological findings**

Histology Outcome	Pre-operative FNAB findings							
	1988 - 1992				1994 - 1998			
	<i>B</i>	<i>I</i>	<i>M</i>	<i>U</i>	<i>B</i>	<i>I</i>	<i>M</i>	<i>U</i>
Histology - benign								
Number of cases	32	21	nil	8	148	99	1	46
Proportion of cases (%)	94.2	67.8	-	100	91.9	75.0	11.1	88.5
Female :Male ratio	3.6	6.0	-	8:0	6.8	8.9	1:0	5.3
Median age (y)	44	50	-	47	49	45	17	51
Histology - PTC								
Number of cases	1	5	1	nil	11	18	7	5
Proportion of cases (%)	2.9	16.1	25.0	-	6.8	13.6	78.8	9.6
Female :Male ratio	1:0	1.5	1:0	-	2.7	8.0	6.0	4.0
Median age (y)	36	41	50	-	45	43	38	48
Histology - Other TC								
Number of cases	1	5	3	0	2	15	1	1
Proportion of cases (%)	2.9	16.1	75.0	-	1.3	11.4	11.1	1.9
Female :Male ratio	0:1	1.5	0.5	-	3:0	1.5	0:1	0:1
Median age (y)	41	41	67	-	59	52	54	59

Table 4.4 Preoperative suspicion of thyroid carcinoma and operative findings for 99 cases of papillary thyroid carcinoma categorized by year of diagnosis.

PTC Characteristics	1978 - 1984		1985 - 1991		1992 - 1998	
	<i>n (%)</i>	<i>M:F</i>	<i>n (%)</i>	<i>M:F</i>	<i>n (%)</i>	<i>M:F</i>
Total Cases	8	1:7	19	1:3.8	72	1:4.5
<i>Thyroid carcinoma unexpected*</i>	3 (37.5)	1:2	8 (42.1)	1:3	32 (44.4)	1:5.4
PTC ≤1.0cm	0	-	3 (15.8)	1:3	17 (23.6)	2:7.5
PTC >3.0cm or Invasive or Metastatic	1 (12.5)	1:0	4 (21.1)	1:3	6 (8.3)	0:6
<i>Thyroid carcinoma expected**</i>	5 (62.5)	0:5	10 (52.6)	1:4	38 (52.7)	1:3.8
PTC ≤1.0cm	2 (25.0)	0:2	2 (10.5)	0:2	12 (16.7)	1:5
PTC >3.0cm or Invasive or Metastatic	1 (12.5)	0:1	4 (21.1)	0:4	15 (20.8)	1:2

Based on response to questionnaire completed by 99 patients with PTC diagnosed between 1978-1998.

* Thyroid carcinoma clinically expected preoperatively

** Thyroid carcinoma not clinically expected preoperatively and identified incidentally at time of thyroidectomy

Figure 4.I Completeness of thyroid carcinoma case ascertainment by Tasmanian Cancer Registry (1988 - 1998)

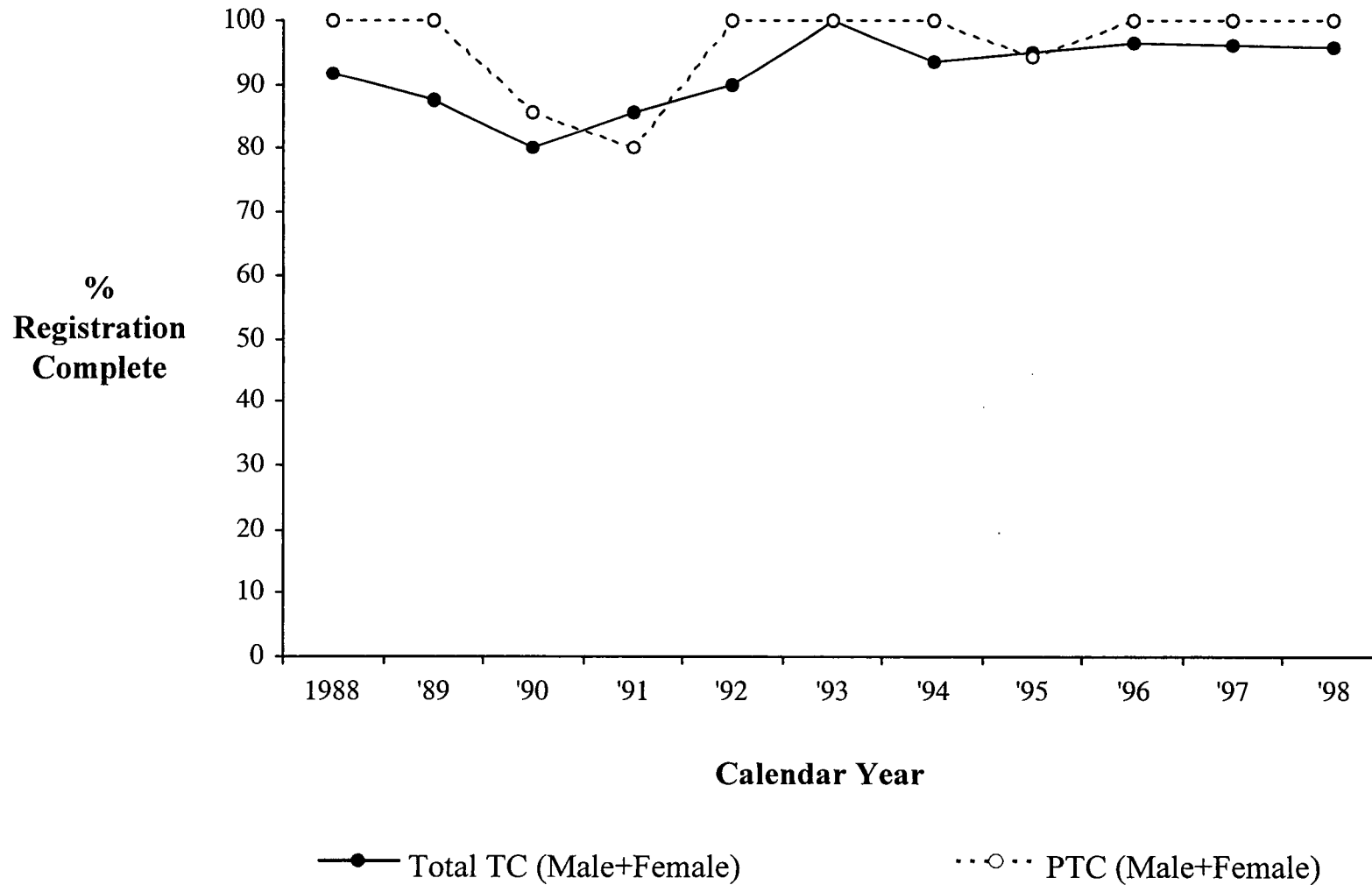


Figure II Trends for Thyroid Surgery and FNAB cytology in Tasmania (1988 - 1998)

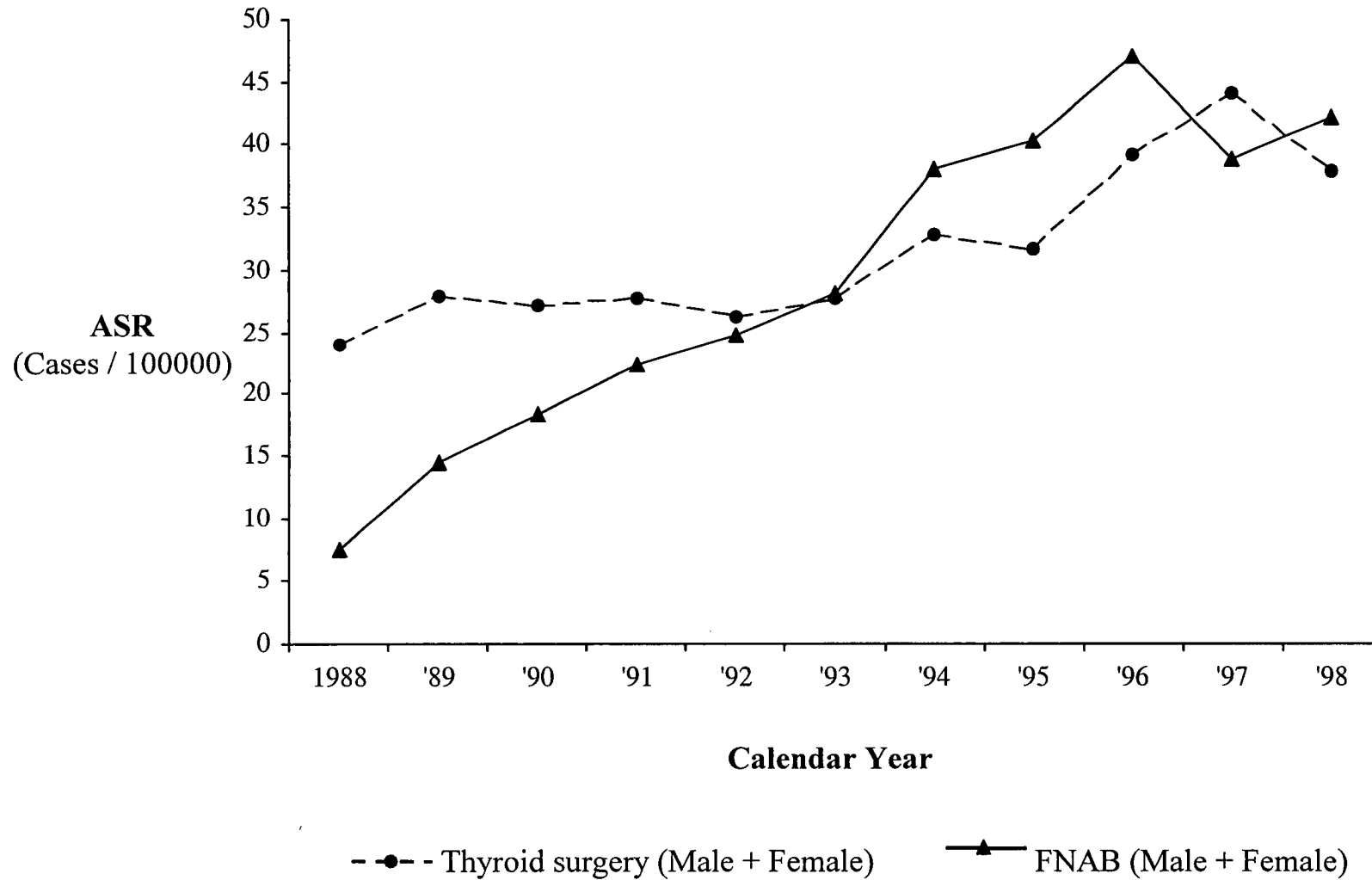
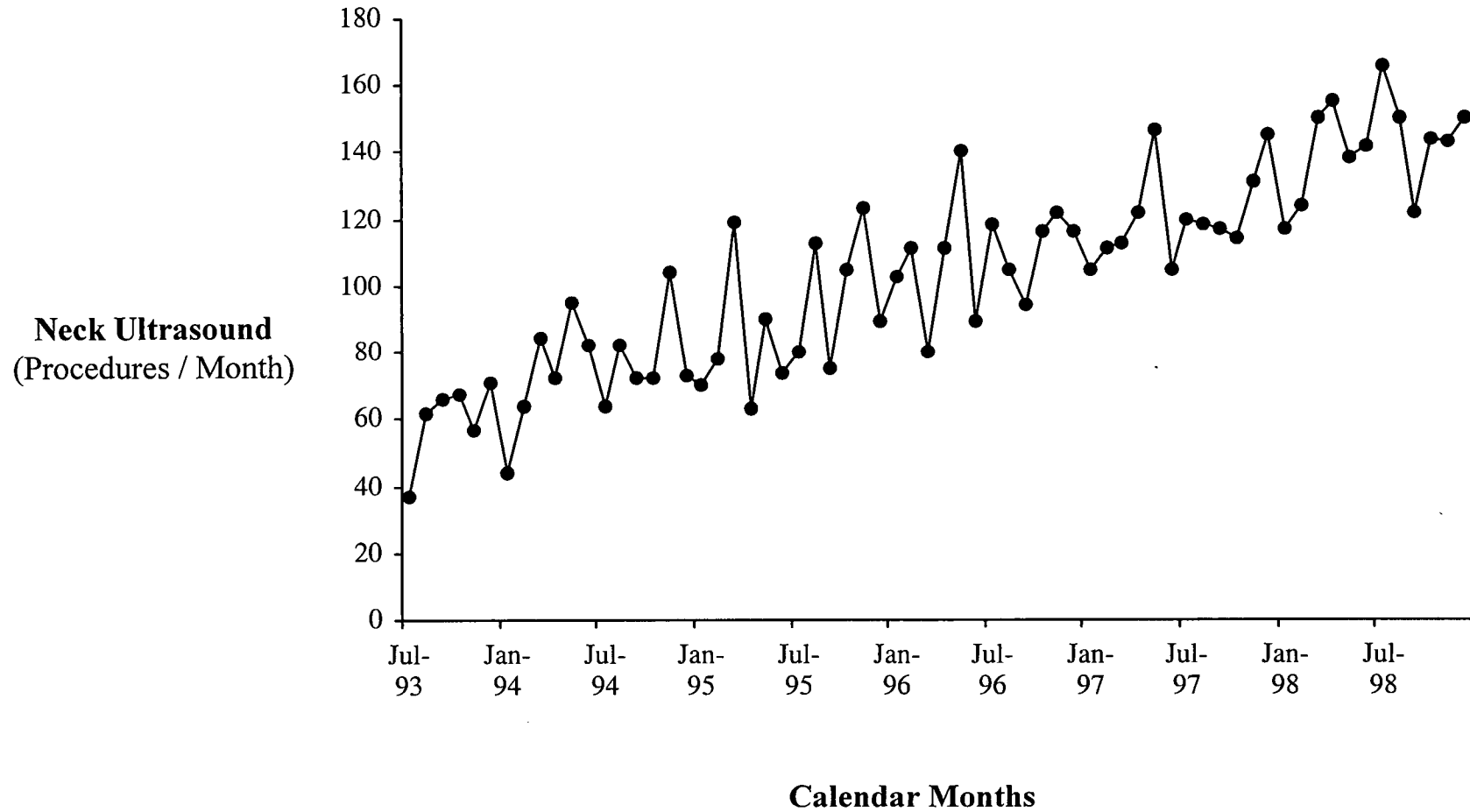


Figure III Trends for Neck ultrasonography in Tasmania (1993 - 1998)



CHAPTER 5

The Impact of Birth and Residence in Tasmania on the Prevalence of Benign and Malignant Thyroid Disease

Prologue

The key questions addressed by this chapter are:

- 1 What is the prevalence of benign and malignant thyroid disease in Tasmania?
- 2 What is the prevalence of subclinical nodular thyroid disease in Tasmania
- 3 Is there evidence for an increased risk for thyroid disease based on birth and subsequent residence in Tasmania?

Presentations and publications arising from this Chapter:

Presented

Preliminary results presented at the 49th meeting of The Endocrine Society of Australia, Gold Coast, Australia, 2006.

The study described in this chapter was undertaken between 1999-2000 prior to introduction of community iodine prophylaxis in 2001.

Aim

- 1 To determine the prevalence of clinically diagnosed benign and malignant thyroid disease in the Tasmanian population.
- 2 To determine the prevalence subclinical thyroid nodularity in the Tasmanian population.
- 3 To determine if longterm residence in Tasmania is associated with an heightened risk for either benign or malignant thyroid disease.

Hypothesis

- 1 More severe historical iodine deficiency in Tasmania relative to other Australian states should manifest as an higher rate of benign and malignant thyroid disease in long-term Tasmanian residents
- 2 Increasing rates for PTC diagnosis in Tasmania and other previously iodine deficient regions of Australia are the result of an high underlying prevalence of both clinical and subclinical benign thyroid disease, resulting in an increased likelihood of diagnosing “occult” PTC.

Introduction

Factors such as genetic susceptibility iodine deficiency and ionising radiation influence the aetiology of goitre, thyroid neoplasia and thyroid dysfunction(28, 29, 133, 136, 206, 222). As discussed in prior Chapters, the influence of iodine nutrition on the pathogenesis and PTC remains poorly understood. Some studies suggest a direct relationship between increasing iodine nutrition and PTC incidence however, the impact age at exposure to iodine deficiency/sufficiency has on PTC risk remains unclear(28, 29, 131, 165, 166, 169).

Iodine deficiency may modify the clinical presentation of benign thyroid disease, thereby increasing the prevalence of goiter and increase the likelihood of diagnosing “occult” PTC by (45, 50, 57). Greater use of ultrasonography and surgery for multinodular goiter evaluation and treatment are likely to accentuate this in iodine deficient populations (71, 173).

In this Chapter an health survey and ultrasonographic study was undertaken to determine the prevalence of both subclinical and previously diagnosed thyroid disease in the Tasmanian population. Specific attention is given to the influences of birth year, birth place, and place of long-term residence on the development of thyroid disease to determine if early life exposure to Tasmanian environmental factors such as iodine nutrition accounts for the contemporary pattern of TC incidence in Tasmania.

Subjects and Methods

Following approval of the Royal Hobart Hospital Research Ethics Committee a random sample of 10 000 adults registered on the Tasmania electoral role in the year 1999 were invited to complete a health questionnaire regarding thyroid disease and related risk factors. The survey was conducted in late-1999 with 5774 respondents available for assessment.

Of these, 463 age stratified respondents were selected at random for invitation to undergo thyroid ultrasonography. Of these, 205 agreed to participate and underwent imaging. Thyroid evaluation was performed by experienced sonographers using a 7.5 mhz transducer. Scanning was undertaken with the subject supine and the neck hyperextended. Thyroid volume (ml) was calculated using the formula: width (cm) x length (cm) x thickness (cm) x 0.479 with the volume of each lobe summed. Goitre was defined as thyroid volume greater than 18.1ml in males and 13.0ml in females(24). Whilst less sensitive than comparison based on body surface area normative criteria, insufficient anthropomorphic data was available to undertake this calculation. The level of early life exposure to the Tasmanian environmental factors such as iodine deficiency was indirectly assessed by two criteria 1) birthplace Tasmania and <1 year lifetime residence elsewhere (High exposure), 2) birthplace not Tasmania and >10 years lifetime residence outside Tasmania (Low exposure).

In addition, patients identified by the Tasmanian Cancer Registry with a diagnosis of PTC during the period 1978-1998 (n=180, Female:Male=3.5, Age at diagnosis 46.4±1.1)

were sought to determine place of birth and long-term residence. Of these, 99 patients (Female:Male=4.8, Age at diagnosis 44.5 ± 1.0) were living, contactable and consented to provide this information.

Normally distributed variables were analysed using the Student's t-test. Where appropriate, numerical data is presented as Mean \pm Standard Error of Mean (SEM). Univariate and multivariate analyses were performed using GraphPad InStat version 3.0a for Macintosh, GraphPad Software, San Diego California USA.

Results

Of 5774 survey respondents (male 2746, female 3028) a past history of TD was reported by 580 (10.0%), (male 106 (3.9%) and female 474 (15.7%)) (*Table 5.1*). An history of thyroid carcinoma was described by 35 (0.6%), (male 10 (0.4%) and female 25 (0.8%)). Goitre was reported by 241(4.2%) (male 47(1.7%), female 194(6.4%)) and an history of thyroid imaging by 238 (4.1%). Thyroxine use was reported by 2.3% of survey respondents (male 12 (0.4%), female 123 (4.1%)); of whom a past history of thyroid surgery and/or goiter was described by 59.3%. Hyperthyroidism was reported by 167 (2.9%), (male 34 (1.2%), female 133 (4.4%)) (*Table 5.1*). Thyroid surgery was described by 162(2.8%) (male 29(1.1%), female 133(4.4%)) of whom, 76 (46.9%) also described an history of thyroid imaging.

Compared to individuals born and resident life-long in Tasmania (n =3150, F:M ratio = 1.2, age = 51.5±0.3 years), those not born in Tasmania and spending more than ten years elsewhere (n=1319, F:M ratio 1.0, age 58.2±0.4 years, mean years lived outside Tasmania 33.2±0.4 years) had a significantly ($p<0.05$) lower prevalence of thyroid problems overall, and goitre in particular (*Table 5.2*). Thyroid cancer was non-significantly increased amongst individuals born and life-long resident in Tasmania (OR=1.3, $p=0.751$) (*Table 5.2*).

Ultrasonography revealed thyroid nodules in 43.4% of individuals undergoing ultrasonography (*Table 5.2, 5.3*). Nodules were at least as frequent in those born and long term resident in Tasmania as for individual born elsewhere (*Table 5.2*). Many

patients (88.8%) with thyroid nodules on ultrasound did not report a previously diagnosed history of thyroid disease (*Table 5.4*).

Stratification of thyroid disease by birth cohort to reflect likelihood of iodine deficiency in childhood/ adolescence is presented in *Table 5.5*. The birth cohort 1925-'40 who were born and resident in Tasmania can be considered relatively iodine deficient in childhood/ adolescence. Childhood/ adolescent, iodine nutrition had improved and was relatively similar irrespective of birthplace and subsequent residence for the 1955-'70 birth cohort due to the nationwide effect of iodophors on iodine nutrition. In a model adjusting for age and gender, only history of "any thyroid disease" ($p=0.002$), goitre ($p=0.002$) and hyperthyroidism ($p=0.024$) were significantly associated with birth and residence in Tasmania for birth cohort 1925-'40. No significant association between thyroid disease and birth and residence in Tasmania was found for birth cohort 1955-'70 (*Table 5.5*).

In a sub-study of an additional 99 PTC patients for whom information regarding place of birth and subsequent residence was available, 57.6% were born in Tasmania and had never resided elsewhere for more than 12 months. There was no correlation between PTC size and patient demographic profile, with 18 of 36 (50.0%) PTC ≤ 1 cm associated with dominant residence in Tasmania compared to 39 of 62 (62.9%) tumours >1 cm diameter (ns).

Discussion

This study indicates that thyroid disorders (including their investigation and treatment) are common, occurring with prevalence similar to that of health problems such as diabetes and hypertension (*Table 5.1*). These findings are similar to those from a large Norwegian population survey of thyroid disease in which hyperthyroidism was reported by 2.5% and 0.6% of females and males respectively and hypothyroidism in 4.8% and 0.9% respectively, and goitre described by 2.9% of females and 0.4% of males(231).

Tasmania's history of relatively more pronounced iodine deficiency appears responsible for the increased likelihood of thyroid disease and thyroid surgery amongst long-term residents born prior to the correction of iodine deficiency. Interestingly, subclinical thyroid nodularity was frequent irrespective of birth place and place of dominant lifetime residence in the 1960's. Similarly, long-term Tasmanian residence did not confer a significantly elevated risk for malignant thyroid neoplasms.

The potential for thyroid ultrasonography to reveal "occult" thyroid nodularity is well *recognised* and highlighted by the current study(41, 60, 173, 232). In accordance with prior research, the prevalence of thyroid nodules on ultrasound was approximately ten-fold higher than that of self reported thyroid disease, with age the key predictor for their presence (*Table 5.2, 5.3*) (50, 57, 60). This confirms the anticipated divergence between the absolute risk for nodular thyroid disease (based on ultrasonography) and the likelihood of clinically diagnosed thyroid nodularity. Notably, whilst the former appears uninfluenced by place of birth and residence, the later was increased amongst individuals

reporting prolonged residence in Tasmania (particularly in their childhood during the iodine deficient era prior to the 1950's).

Whilst the current results supports the well established link between iodine deficiency and goitre (simple, multinodular and functionally autonomous), they do not show a significant association between the absolute risk for development of nodular thyroid disease / neoplasia and iodine nutrition. Age as opposed to unique environmental factors appears to be the key determinant of absolute prevalence of thyroid nodularity.

Thyroid carcinoma was non-significantly higher for in individuals born and resident long term in Tasmania versus those born elsewhere. However, there was no convincing evidence for a specific environmental exposure (such as iodine nutrition) to explain PTC incidence trends. The birth cohort born after introduction of iodine supplementation/iodophors appear to be at no greater risk of thyroid disease irrespective of place of birth residence(214, 216). This suggests that the pathogenesis of PTC is not influenced by the absolute increase (greatest in Tasmania) in iodine nutrition. However, the relative comparison methodology used by this study does not account for possible shared exposure to common PTC risk factors affecting both those born and resident long-term in Tasmania as well as those migrating to Tasmania from elsewhere.

The influence of early life iodine nutrition on thyroid neoplasia could be underestimated by this study if: a) the historical differential in severity of iodine deficiency between Tasmania and the other south-eastern Australian states was less pronounced than generally assumed, b) the assumption that migrants to Tasmania derived predominantly

from relatively iodine sufficient regions is incorrect (eg. post second world war migration from iodine deficient regions of Europe), and c) common levels of iodine nutrition across Australia in more recent years have modified the impact any difference in childhood iodine nutrition may have had on nodular thyroid disease and thyroid volume. It is also notable that whilst the relative increase in TC incidence is highest in previously iodine deficient regions of Australia, the absolute incidence of PTC in these areas was lower at baseline. Hence iodine repletion via milk during the 1960's-1980's may have relatively affected PTC incidence more in previously deficient areas.

Whilst the results from the current study are prone to bias (self-reported medical history is influenced by the disease in question and the temporal proximity of disease occurrence to time of survey), thyroid diseases have been shown to be moderately well reported by self-administered questionnaire compared to in-person interview. In the study by Brix *et al* the self-reported diagnosis of hyperthyroidism and hypothyroidism were both 98% although the specificity was mediocre at 57% and 67% respectively(233). Similarly, an assessment of self-reported cancer incidence in the California Teachers Study found the concordance for thyroid cancer between survey results and cancer registry data was at least 90% sensitive and specific (234).

Conclusions

This study confirms that neck imaging has a great capacity to increase identification of subclinical nodular thyroid disease and that residence in a region with an history of iodine deficiency increases the likelihood of neck imaging and surgery for benign conditions. Furthermore, injudicious use of thyroid ultrasonography in patients without clinical suspicion of thyroid disease could be considered a “risk factor” for thyroid surgery and consequently the diagnosis of prevalent, yet clinically not apparent, papillary microcarcinoma.

A direct link between iodine nutrition and the pathogenesis of PTC in Tasmania is not suggested by this study. However, further evaluation of the role played by other established risk factors such as ionising radiation and genetic susceptibility will be of value.

Table 5.1 Thyroid and health profile of study participants

Characteristics	All questionnaire respondents		Ultrasound sub-study	
	Male	Female	Male	Female
Number of Subjects	n=2746	n=3028	n=76	n=129
Age (yrs)	54.7±0.3	52.5±0.3	55.7±1.7	50.2±1.0
Any past history thyroid disease (%)	3.9	15.7	2.6	13.2
Goitre (%)	1.7	6.4	1.3	5.4
Thyroid surgery (%)	1.1	4.4	0.0	2.3
Thyroid cancer (%)	0.4	0.8	0.0	0.0
Thyroid scan (%)	1.7	6.3	0.0	8.5
Hyperthyroid (%)	1.2	4.4	1.3	3.9
Hypothyroid (%)	1.1	5.8	1.3	3.9
Taking thyroxine (%)	0.4	4.1	0	2.3
Family History thyroid disease (%)	10.4	21.1	15.8	27.1
Hypertension (%)	24.3	27.9	18.4	20.9
Diabetes (%)	5.3	4.5	8.3	3.9
Hypercholesterolaemia (%)	16.7	13.1	13.2	9.3

**Table 5.2 Prevalence of clinical and subclinical nodular thyroid disease for
questionnaire respondents undergoing thyroid ultrasonography**

Ultrasonographic Characteristics	Age 18-44 years		Age 45-64 years		Age 65-85 years	
	<i>Past History TD*</i>	<i>No Past History TD**</i>	<i>Past History TD*</i>	<i>No Past History TD**</i>	<i>Past History TD*</i>	<i>No Past History TD**</i>
Number of subjects (n=)	6	62	8	82	5	42
Female / Male ratio	6/0	1.8	7.0	2.4	4.0	0.6
Age (yrs)	42.6±0.6	37.9±0.6	53.0±2.4	53.0±0.6	72.2±2.1	71.0±0.6
Thyroid volume (ml)	6.0±2.3	10.2±0.7	7.3±1.6	9.8±0.6	10.5±2.1	11.8±0.9
Nodules (total) (%)	16.7	30.7	50.0	43.9	80.0	57.1
Solitary nodule (%)	16.7	12.9	12.5	12.2	0.0	16.7
Multiple nodules (%)	0.0	17.7	37.5	31.7	80.0	40.5
Nodule size						
- <1cm (%)	16.7	27.4	37.5	37.8	60.0	47.6
- 1-2cm (%)	0.0	9.7	12.5	18.3	20.0	26.2
- >2cm (%)	0.0	0.0	0.0	1.2	0.0	4.8

* Any past history of thyroid disease (goitre, nodules, surgery, thyroid dysfunction or imaging) reported by patient
** No past history of thyroid disease reported by patient

Table 5.3 Prevalence of thyroid disease based on place of birth and childhood residence for questionnaire respondents and subjects undergoing thyroid ultrasonography

Characteristic	Female			Male		
	<i>Born in Tas. <1y Elsewhere**</i>	<i>Not Born in Tas. >10y Elsewhere^</i>	<i>p=</i>	<i>Born in Tas. <1y Elsewhere**</i>	<i>Not Born in Tas. >10y Elsewhere^</i>	<i>p=</i>
Questionnaire						
Number of subjects (n=)	n=1727	n=650		n=1423	n=669	
Age (yrs)	51.1±0.4	56.7±0.6	<0.001	51.9±0.5	59.6±0.6	<0.001
Years lived away Tas. (yrs)*	-	32.3±0.6	na	-	34.0±0.6	na
Any past thyroid disease (%)	16.6	13.5	0.082	4.3	2.5	0.066
Goitre (%)	7.4	4.5	0.013	2.5	0.7	0.013
Thyroid surgery (%)	4.5	3.8	0.547	1.3	0.7	0.404
Thyroid cancer (%)	0.9	0.6	0.719	0.4	0.4	0.930
Thyroid scan (%) ***	5.6	6.6	0.410	1.3	1.5	0.928
Hyperthyroid (%)	4.6	2.9	0.091	1.1	1.2	0.886
Hypothyroid (%)	5.7	6.2	0.770	1.2	0.7	0.481
On thyroxine (%)	3.9	4.0	0.944	0.6	0.3	0.635
Family History TD (%) ^^	23.6	14.5	<0.001	11.1	9.0	0.157
Ultrasonography						
Number of subjects (n=)	n=71	n=32		n=38	n=20	
Age (yrs)	47.7±1.3	58.0±2.0	<0.001	52.8±2.6	61.8±3.1	<0.001
Years lived away Tas. (yrs)*	-	32.9±2.5	na	-	35.0±3.7	na
Thyroid volume (ml)	8.6±0.6	9.7±0.8		12.7±0.8	11.2±1.2	
Goitre (%)	14.1	18.8	0.756	13.2	15.0	0.847
Nodules (total) (%)	46.5	62.5	0.196	28.9	40.0	0.577
Solitary nodule (%)	11.3	12.5	0.857	13.2	15.0	0.847
Multiple nodules (%)	35.2	50.0	0.230	15.7	25.0	0.618
Nodule size						
- <1cm (%)	39.4	56.3	0.169	26.3	40.0	0.440
- 1-2cm (%)	15.5	25.0	0.381	10.5	10.0	0.950
- >2cm (%)	2.8	3.1	0.931	0	0	na

* Number of years of residence away from Tasmania

** Born in Tasmania and never lived elsewhere for more than 12 months

^ Not born in Tasmania and has lived elsewhere for more than 10 years

*** History of ever undergoing any thyroid imaging reported by patient

^^ Family history of thyroid disease (TD) reported by patient

ns p values >0.1 reported as ns

**Table 5.4 Prevalence of thyroid disease based on age for questionnaire respondents
and subjects undergoing thyroid ultrasonography**

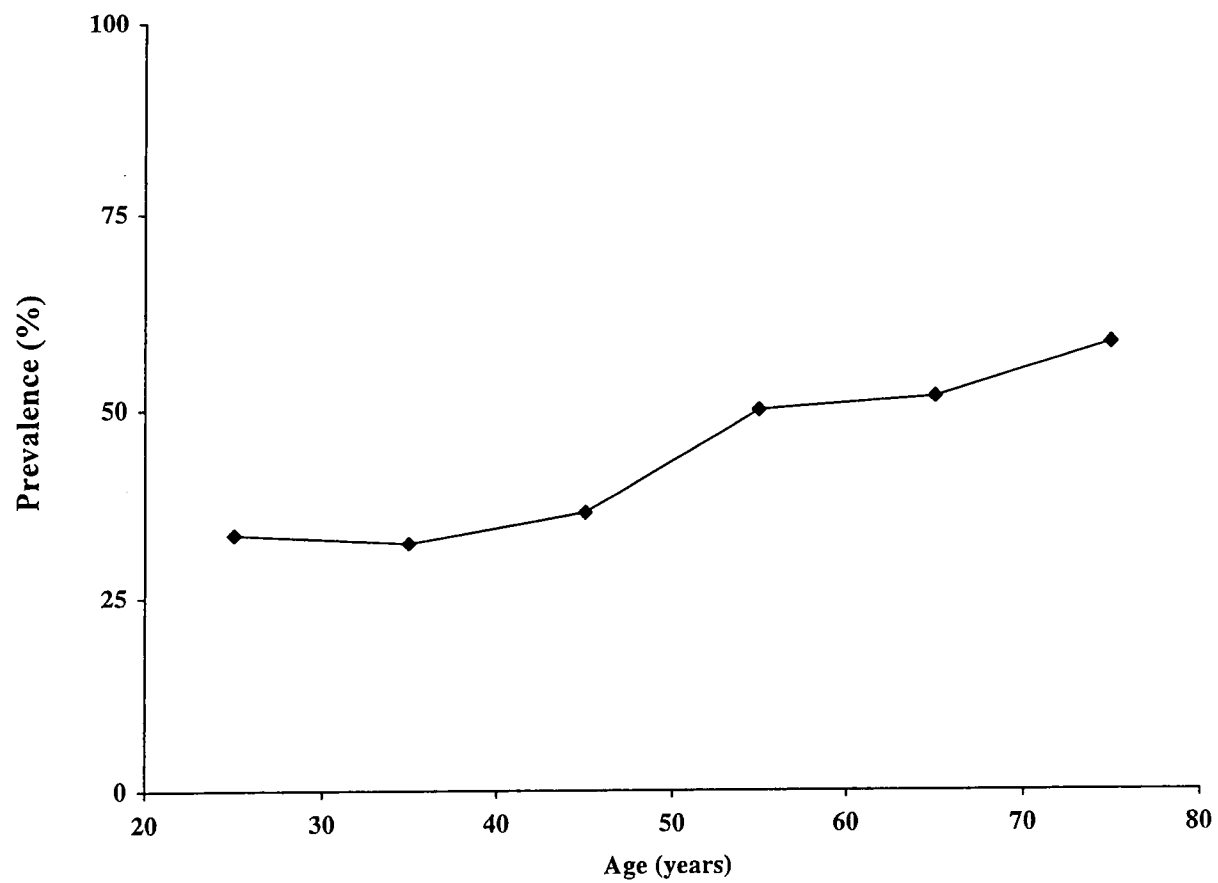
Characteristics	Age 18-44 years		Age 45-64 years		Age 65-85 years	
	Male	Female	Male	Female	Male	Female
Questionnaire						
Number of subjects (n=)	n=808	n=1065	n=1012	n=1089	n=924	n=869
Age (yrs)	33.7±0.3	33.2±0.2	55.0±0.2	54.7±0.2	72.7±0.2	73.4±0.2
Any past thyroid disease (%)	2.5	7.6	3.2	16.8	5.8	24.2
Goitre (%)	1.7	3.5	1.3	6.3	2.2	10.1
Thyroid surgery (%)	0.7	1.7	0.8	5.3	1.6	6.6
Thyroid cancer (%)	0.4	0.8	0.3	1.0	0.4	0.7
Thyroid scan (%)**	1.1	3.9	2.2	6.9	1.7	8.5
Hyperthyroid (%)	1.1	2.8	0.9	3.9	1.7	7.0
Hypothyroid (%)	0.5	3.4	1.4	6.2	1.3	8.2
On thyroxine (%)	0.0	1.9	0.4	5.2	0.9	5.3
Family History TD (%)***	11.4	20.6	10.1	23.8	10.0	18.4
Born in Tasmania (%)***	80.1	79.6	65.6	68.2	64.3	64.3
Ultrasonography						
Number of subjects (n=)	n=22	n=46	n=26	n=64	n=28	n=19
Age (yrs)	37.3±1.1	38.8±0.7	54.4±0.9	52.4±0.7	71.4±0.7	70.7±0.9
Thyroid volume (ml)	13.1±1.3	8.2±0.6	11.7±1.2	8.8±0.7	12.4±1.1	10.5±1.1
Goitre (%)	13.6	10.9	15.4	12.5	17.9	26.3
Nodules (total) (%)	22.7	34.8	19.2	56.3	50.0	73.7
Solitary nodule (%)	13.6	15.2	7.7	14.1	17.9	10.5
Multiple nodules (%)	9.0	19.6	11.5	42.2	32.1	63.2
Nodule size						
- <1cm (%)	22.7	30.4	19.2	46.9	42.9	57.9
- 1-2cm (%)	4.6	10.9	3.9	23.4	25.0	26.3
- >2cm (%)	0.0	0.0	0.0	1.6	0.0	10.5

* Family history of thyroid disease (TD) reported by patient
** History of ever undergoing any thyroid imaging reported by patient
*** Born in Tasmania and never lived elsewhere for more than 12 months

Table 5.5 Age and birth cohort stratified prevalence of thyroid disease based on place of birth and childhood residence for questionnaire respondents and subjects undergoing thyroid ultrasonography

Characteristic	Birth Years 1955 –‘70			Birth Years 1925 –‘40		
	<i>Born in Tas. <1y Elsewhere</i>	<i>Not Born in Tas. >10y Elsewhere</i>	<i>p=</i>	<i>Born in Tas. <1y Elsewhere</i>	<i>Not Born in Tas. >10y Elsewhere</i>	<i>p=</i>
Questionnaire						
Number of subjects (n=)	775	229	-	895	512	-
Age (yrs)	37.1±0.2	37.80.3	0.06	66.5±0.2	67.1±0.2	0.032
F/M	1.3	1.4	0.649	1.0	0.8	0.052
Years lived away Tas. (yrs)	-	25.8±0.5	na	-	36.5±0.7	na
Any past thyroid disease (%)	5.0	10 (4.4	0.813	17.1	8.6	<0.001
Goitre (%)	2.6	2.6	0.974	8.3	2.7	<0.001
Thyroid surgery (%)	1.3	1.3	0.982	4.5	1.6	0.006
Thyroid cancer (%)	0.5	0.4	0.881	0.2	0.2	0.912
Thyroid scan (%)**	2.5	3.5	0.533	5.1	3.9	0.357
Hyperthyroid (%)	1.9	1.3	0.731	4.8	1.8	0.006
Hypothyroid (%)	2.3	2.2	0.902	5.3	4.1	0.402
On thyroxine (%)	1.3	0.9	0.870	3.5	1.8	0.092
Family History TD (%)***	15.9	12.2	0.211	18.3	10.2	<0.001
Ultrasonography						
Number of subjects (n=)	43	7		19	22	
Age (yrs)	38.5±0.6	41.8±1.1	0.042	65.8±1.2	67.9±0.7	0.124
F/M	1.8	6.0	0.518	0.7	1.8	0.287
Years lived away Tas. (yrs)	-	25.1±4.2	na	-	37.6±3.7	na
Goitre (%)	11.6	0.0	0.786	21.1	18.2	0.817
Nodules (total) (%)	32.6	42.9	0.677	52.6	63.6	0.693
Solitary nodule (%)	11.6	14.3	0.841	15.8	13.6	0.849
Multiple nodules (%)	20.9	28.6	0.651	36.8	50.0	0.595
Nodule size						
- <1cm (%)	32.6	42.9	0.677	42.1	59.1	0.440
- 1-2cm (%)	7.0	14.3	0.464	21.1	18.2	0.817
- >2cm (%)	0.0	0.0	na	10.5	4.6	0.895

Figure 5.1 Prevalence of thyroid nodules by age (10 year age categories)



CHAPTER 6

**An indirect assessment of the role of ionising radiation in the
genesis of contemporary PTC incidence trends**

Prologue

The key questions addressed by this chapter are:

- 1 Is there molecular genetic evidence (*RET/PTC1* rearrangement) for past ionizing radiation exposure in priming Tasmanian PTC incidence trends?
- 2 What are the prevalence trends for *RET/PTC1* in Tasmanian PTC?

Presentations and publications arising from this Chapter:

Presented

Preliminary results presented at the International Congress of Endocrinology (ICE 2000), Sydney, Australia, 2000.

Published

Burgess JR, Skabo S, McArdle K, Tucker P. Temporal trends and clinical correlates for the *ret/PTC* mutation in papillary thyroid carcinoma. *ANZ J Surg.* 2003; 87: 31-5.

In accordance with the criteria for submission of thesis by previously published research, Chapter 6 is based on the above cited publication.

Aim

To determine if evidence exists for past ionizing radiation exposure as a cause for increasing PTC incidence.

Hypothesis

- 1 Childhood exposure to radioiodine during the 1950's and early 1960's contributes to contemporary PTC incidence trends.
- 2 Time trends for the *RET/PTC1* rearrangement may provide an indirect indication of past ionizing radiation exposure as an aetiological factor in contemporary PTC incidence trends.

Introduction

Ionizing radiation is the best characterized aetiological factor for thyroid neoplasia (134, 136, 206, 235). Benign and malignant tumours are predisposed by prior thyroid irradiation. PTC is the most frequent malignant sequel of thyroidal irradiation (133, 136, 206). There appears to be no threshold below which thyroid tumorigenesis is not increased, but the risk is greatest when the exposure occurs during childhood, particularly during the early years of life (135-137, 206). Although exposure in early childhood confers the greatest risk, disease may not arise until adulthood because the latency between exposure and cancer presentation can exceed three decades (133, 136, 137, 209).

Both external beam irradiation and ingestion of radioiodines in childhood are associated with PTC development (134, 136). In the case of radioiodine, even low levels of exposure from nuclear fallout can marginally increase long-term thyroid cancer risk (133, 136, 137, 209). It has been estimated that fallout radioiodines from Chernobyl increased thyroid cancer incidence as far away as Connecticut in the USA (139). When the low baseline incidence of PTC is considered in conjunction with the size of fallout-exposed populations, significant relative increases in PTC incidence are a potential long-term consequence of exposure to low levels of radioiodine fallout.

A number of genes are linked to the development of PTC, including *RAS*, *RET/PTC*, *TRK*, *BRAF*, *p53*, *MET* and *PAX8* (49, 109, 110, 115-117). Activating mutations involving *RET*, a proto-oncogene encoding a receptor tyrosine kinase, can arise following thyroidal irradiation (121, 124). Fusion of *RET* to the promoter region of an unrelated gene gives rise to mutations collectively termed *RET/PTC* rearrangements (119, 130).

The most prevalent of these are *RET/PTC1* and *RET/PTC3* (119, 126, 127). Both mutations result from inversions involving the long arm of chromosome 10 (121, 124, 130). High levels of radioiodine fallout following the Chernobyl accident produced an early and overt rise in PTC, which was associated with the *RET/PTC3* rearrangement (115, 121, 130). However, subsequent studies have also shown *RET/PTC1* to be associated with PTC developing after a long latency(>10 years) from the time of radiation exposure (115, 124, 130).

Therefore, the *RET/PTC1* rearrangement may occur at higher frequency in thyroid neoplasms arising after exposure to ionizing radiation, particularly in tumours developing following a long latency after irradiation (115, 121, 124, 236). The *RET/PTC1* rearrangement has also been associated with tumour behaviour and prognosis. Some studies have suggested an association with a relatively benign clinical pattern of disease (111, 119, 129, 130).

The influence of past exposure to radioiodine and diagnostic X-rays on contemporary Australian PTC incidence trends is difficult to establish given the absence of exposure data. Although *RET/PTC1* is not specific to PTC arising after radiation exposure, prevalence trends for *RET/PTC1* in PTC may provide insights into the role of past ionizing irradiation in the recent rise in national PTC incidence(115, 124).

In this chapter temporal trends and the clinicopathological associations for *RET/PTC1* rearrangement in PTC diagnosed in Tasmania during the years 1978-1998 are assessed.

Subjects and Methods

Following approval from the Tasmanian Cancer Registry Data Release Committee and the Royal Hobart Hospital Research Ethics Committee, all cases of PTC recorded by the Registry during the period 1978-1998 were identified and tissue samples sought for analysis.

A study sample of 98 cases, representing all cases of PTC diagnosed during the even numbered years from and including 1978-1998, was defined. Pathology laboratories around Tasmania were contacted and 62 paraffin-embedded tumour samples were located. The histology of each sample was reviewed by two histopathologists to confirm accuracy of the original diagnosis (213).

Ten tissue sections of 5 μ m thickness were cut from representative areas of each paraffin-embedded tissue block. Samples were deparaffinized by a 10-min incubation with xylene followed by a two-stage 100% ethanol wash. Deparaffinized samples then underwent an overnight (16-h) protease tissue digestion using the DNeasyTM Tissue Kit (Qiagen, Valencia, CA, USA) standard -protocol. The RNA and DNA were coextracted from digested samples using the DNeasyTM Tissue Kit (Qiagen) protocol. An additional on-column DNAase digestion was then used to ensure that the eluted material was free from DNA contamination.

Reverse transcription-polymerase chain reaction (RT-PCR) for *RET/PTC1* was performed using the One-Step RT-PCR Kit (Qiagen) reagents and standard protocol. The

RNA from the TPC-1 cell line was used as the positive control. A negative control (H₂O) was included for each primer pair in every RT-PCR run. The primers used to detect the *RET/PTC1* rearrangement were as described by Nikiforov *et al.* (5'-GCTGGAGACCTACAAACTGA-3' (nucleotides 425-443) and 5'-GTTGCCTTGACCACTTTTC-3' (nucleotides 661-685)) (121). Overall RNA integrity was assessed by RT-PCR using primers for human hypoxanthine phosphoribosyltransferase (5'-CCTGCTGGAT-TACATCAAAGCACTG-3'(nucleotides 316-340) and 5'-CCTGAAGTATTCATTATAGTCTCAAGG-3' (nucleotides 661-685)] (236).

One microgram of total RNA was used in each reaction. Reverse transcription was carried out at 50°C for 30 min followed by a 95°C, 10-min denaturation step. Amplification consisted of 42 cycles of denaturation at 94°C for 45s, annealing at 56°C for 1 min, followed by a final 10-min extension step at 72°C.

The RT-PCR products were separated by electrophoresis on agarose gel and visualized using the ethidium bromide technique prior to photographic documentation (*Fig. 6.2*). The identity of products positive for hypoxanthine-guanine phosphoribosyltransferase (HPRT) and *RET/PTC1* and each of the positive controls was confirmed by sequencing (ABI Prism DNA sequencing kit and ABI PRISM 377 DNA sequencer; Applied Biosystems, Foster City, CA, USA).

In addition, patients identified by the Tasmanian Cancer Registry with a diagnosis of PTC during the period 1978-1998 (n=180, Female:Male=3.5, Age at diagnosis

46.4±1.1years) were sought to determine history of past head and neck irradiation. Of these, 99 patients (Female:Male=4.8, Age at diagnosis 44.5±1.0years) were living, contactable and consented to provide this information.

Data were analysed using the Student's *t*-test for normally distributed variables and the chi-squared test for non-parametric data. Where appropriate numerical data are presented as mean ± SD.

Results

The *RET/PTC1* mutation was found in 26 (63%) tumours. Forty-three per cent of male patients and 68% of female patients were positive. The mean age at diagnosis for *RET/PTC1*-positive and *RET/PTC1*-negative tumours was 46.5 ± 15.46 and 41.9 ± 13.45 years, respectively. The *RET/PTC1* mutation was significantly associated with larger tumour size (*Table 6.1*). The *RET/PTC1* mutation was not associated with an adverse prognosis (*Table 6.1*).

The prevalence of tumours positive for *RET/PTC1* remained stable over the study period (*Table 6.1*). Tumours positive for *RET/PTC1* did not exhibit birth year or diagnosis year clustering (*Table 6.1; Fig. 6.3*). Similarly, *RET/PTC1* positivity was not associated with other clinicopathological characteristics such as presence of multinodular goitre, lymphocytic infiltration, tumour multicentricity or PTC histological subtype (*Table 6.1*).

Of the 99 PTC patients who provided information regarding head and neck irradiation, 4 (4.0%) had a past history of this. Two cases related to treatment of haematological malignancies, one for naevus, and the fourth for a brain tumour. Of these, only one (the naevus) was associated with childhood radiotherapy.

Discussion

In comparison with studies undertaken in other countries, this study identified a relatively high prevalence for the *RET/PTC1* re-arrangement in Tasmanian PTC specimens (130). However, it is consistent with the findings previously reported by Chua *et al.* who described a prevalence of 55% for *RET/PTC1* in tumours treated at a Sydney teaching hospital (237). However, another Australian study by Learoyd *et al.* also studied this issue and reported a prevalence for *RET/PTC1* of 8% (120).

Chua *et al.* also studied PTC from New Caledonia and found a similar frequency of the *RET/PTC1* rearrangement (70%) compared to that observed in NSW (85%) (237). This is notable given the high rate of PTC incidence New Caledonia (237, 238). One could speculate that tumours from New Caledonia might have a higher rate of the *RET/PTC1* rearrangement than Australian tumours due to the potential for higher levels of past exposure to radio-iodine fallout (149). The failure to find a difference between these populations suggests either: (i) any difference in exposure of the New Caledonian population relative to that of NSW is not reflected by *RET/PTC1* prevalence; (ii) the high prevalence of *RET/PTC1* in NSW samples may indicate a role for past ionizing irradiation in this Australian population; or (iii) *RET/PTC1* is of little or no value as a radiation signature.

Iodine deficiency increases thyrocyte uptake of radioiodines such as I131, potentially increasing the likelihood of subsequent neoplasia (144). Mild-to-moderate iodine deficiency affected Tasmania as well as much of coastal Victoria, New South Wales and southern Queensland prior to the early 1960s (214, 225). The current rise in PTC incidence in Australia has been most marked for the population residing on Australia's eastern seaboard, particularly those regions with a history of iodine deficiency (213, 228).

Prior to the Universal Test Ban Treaty of 1962, atmospheric nuclear weapons testing during the 1950s and early 1960s resulted in numerous episodes of fallout throughout Australia (*Figure 6.1*). Although direct human exposure to radioiodine from environmental contamination of air, soil and water is likely to have been negligible, cows' milk is recognised as a vector for radioiodine entering the food chain (144). In Australia, contamination of this food source by radioiodine was documented by Van Middlesworth and Melick in the 1950s-1960s. Their research found that episodes of I131 fallout affected grazing livestock in South Eastern Australia (147, 239).

Evidence for a relationship between *RET/PTC1* prevalence and birth cohort was sought in the present study (*Table 6.1*). Although exposure of the Australian population to low levels of radioiodine fallout can be inferred from the available data (*Figure. 6.1*), the current findings do not demonstrate an overt relationship between contemporary PTC incidence trends and the occurrence of *RET/PTC1* rearrangements (147, 239).

When assessing the possible aetiological role of a risk factor in individual cases of disease, proof of causation is virtually impossible to establish in the absence of either a

direct or surrogate measure of past exposure to that risk factor. While not excluding ionizing radiation of the Australian population during the 1950s and early 1960s as a cause for the contemporary rise in PTC incidence, clear support for this hypothesis is not provided by the current study. Nonetheless, this is the first study to specifically examine temporal trends for PTC, and it shows a stable prevalence for *RET/PTC1* despite a concurrent rise in PTC incidence.

The present study shows a significant clinicopathological association for the *RET/PTC1* rearrangement. Tumours positive for the *RET/PTC1* rearrangement were of larger size and more likely to exhibit lymph node metastases than those without the mutation. However, this trend was not associated with an increased risk for mortality. These observations are in keeping with the existing literature that suggests that *RET/PTC1* does not confer heightened tumour aggressiveness (130).

The *ret/PTC 1* rearrangement appears to be a relatively early event in PTC development(130). This could explain the apparent contradiction of the rearrangement being common in both “occult” papillary microcarcinoma, radiation induced PTC and follicular adenomas(130). In each case, the early events that initiate tumor formation may involve *ret/PTC 1*, but tumour progression requires accrual of additional oncogenic mutations. Thus, if *RET/PTC1* positive tumours acquire concurrent mutations, such as inactivation of the p53 tumour suppressor gene, a more aggressive phenotype may develop.

The success of RT-PCR is greatly affected by amplicon size (130, 237). The greater the size, the greater the chance of false negative results due to sample degradation during

RNA extraction. This is particularly so when RT-PCR is performed on RNA derived from paraffin-embedded tissue samples. In the study by Learoyd *et al.*, which reported an 8% *RET/PTC1* prevalence, the amplicon was substantially larger than that sought by the primer set used both in the present study and that of Chua *et al* (120, 237). Thus methodological factors are likely account for the divergent findings of these three Australian studies.

Conclusions

This is the first study to map time trends for the prevalence of *RET/PTC1* relative to PTC incidence patterns. There was no clear relationship between PTC incidence trends and *RET/PTC1* prevalence to suggest ionising irradiation was a dominant factor in the genesis of recent PTC incidence trends. Whilst in some circumstances the *RET/PTC1* rearrangement might be an indirect indication of past radiation damage, it may not be sufficiently specific to be considered a radiation signature. However, the absolute prevalence of *RET/PTC1* (63%) is greater than that reported in many prior studies and is consistent with levels found in irradiated populations. Further assessment of past radiation exposure using alternate methodologies is required.

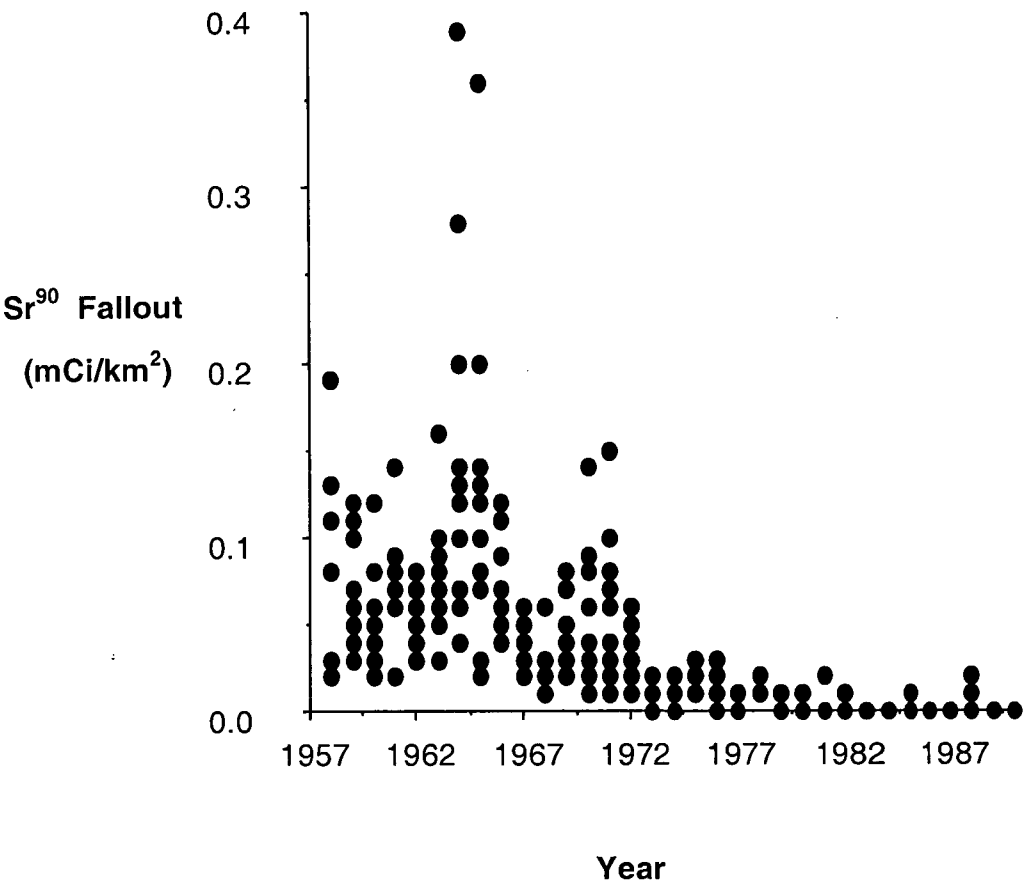
Table 6.1 **Clinicopathological correlates of *RET/PTC1* positive papillary thyroid carcinoma diagnosed in Tasmania between 1978 and 1998**

Characteristic	<i>RET/PTC1</i> (+) (n)	<i>RET/PTC1</i> (-) (n)	Odds ratio (95% CI)	P value
Total (n=)	26	15		
Age \geq 45 years	13 (50%)	6 (40%)	1.5 (0.6-2.6)	0.746
Multinodular goitre	11 (42%)	5 (33%)	1.3 (0.6-3.0)	0.742
Lymphocitic thyroiditis	9 (35%)	8 (53%)	0.5 (0.1-1.7)	0.328
Sclerosing variant	3 (12%)	2 (13%)	0.9 (0.1-5.8)	1.000
Follicular variant	8 (31%)	2 (13%)	2.9 (0.5-16.0)	0.277
Multicentric tumour	5 (19%)	3 (20%)	1.0 (0.2-4.7)	1.000
Family history of PTC	1 (3.9%)	nil	1.8 (0.1-48.0)	1.000
Extra-thyroid invasion	7 (27%)	1 (7%)	5.2 (0.6-47.0)	0.220
Metastases present	5 (19%)	1 (7%)	3.3 (0.4-32.0)	0.388
Death<1 year post Dx	2 (8%)	3 (20%)	0.3 (0.1-2.3)	0.337
Size \leq 1.0cm	7 (27%)	8 (53%)	0.3 (0.1-1.2)	0.108
Size >1cm	19 (73%)	7 (47%)	3.1 (0.8-12)	0.108
Size >2	13 (50%)	nil	31 (1.7-570)	0.001
Diagnosed < 1994	11 (42%)	7 (47%)	0.8 (0.2-3.0)	1.000
Diagnosed \geq 1994	15 (58%)	8 (53%)	1.2 (0.3-43.0)	1.000

CI - confidence interval

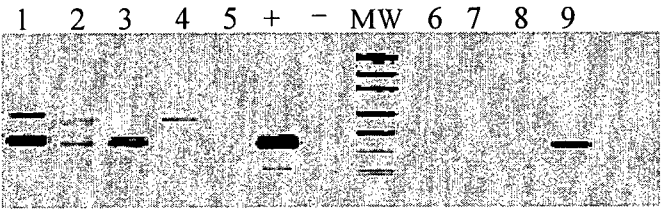
Death<1 year post Dx - death within one year of PTCdiagnosis

Figure 6.1 Strontium-90 fallout in Hobart, Tasmania 1958-1990



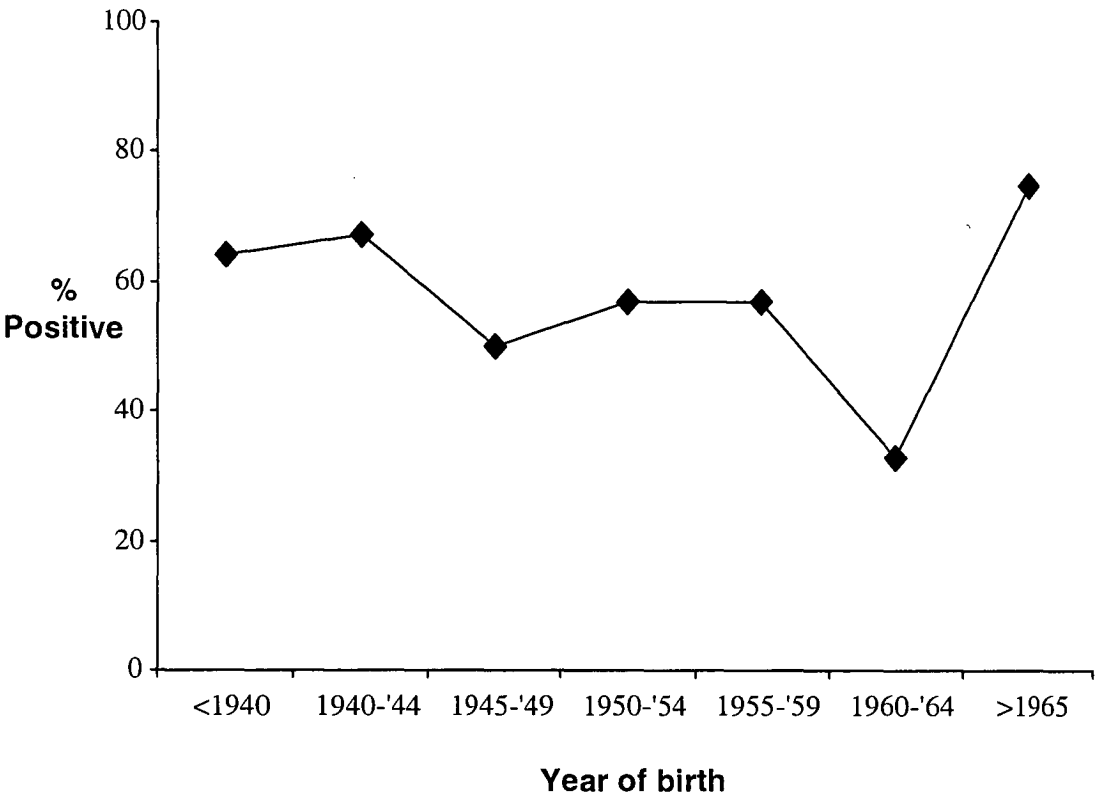
Data from the Fallout Measurements Database, Environmental Measurements Laboratory, Office of Environmental Management, United States Department of Energy.
http://www.eml.doe.gov/databases/fallout/fallout_data_search.htm
Closed circles represent the level of Sr^{90} Fallout during the individual calendar months of the year.

Figure 6.2 Representative examples of *RET/PTC1* analysis



+ Positive control
- Negative control
MW Molecular weight markers
Lanes 1-9 Tumour samples

Figure 6.3 Birth year distribution of ret/PTC positive PTC



Chapter 7

Heritable susceptibility to papillary carcinoma of the thyroid

PROLOGUE

The key questions addressed by this chapter are:

- 1 Does heritable susceptibility contribute to the incidence of PTC in Tasmania?
- 2 What is the inheritance pattern of familial PTC?

Presentations and publications arising from this Chapter:

Published

Burgess JR, Wilkinson R, Ware R, Greenaway TM, Percival J, Hoffman L. Two families with an autosomal dominant inheritance pattern for papillary carcinoma of the thyroid. *J. Clin. Endocrinol. Metab.* 1997; 82: 345-348.

In accordance with the criteria for submission of thesis by previously published research, Chapter 7 is based on the above cited publication.

Aim

To assess the prevalence and inheritance pattern of familial PTC in Tasmania

Hypothesis

- 1 Germline mutations modulate the risk for developing PTC.
- 2 A founder effect does not account for the relatively high incidence of PTC in Tasmania.

Introduction

Understanding the role of germline mutations in modulating PTC risk is of interest for numerous reasons. It opens an avenue for understanding the pathogenesis of PTC, as well as influencing clinical management decisions (159). Familial diseases arising in founder populations also have the potential to influence apparent disease incidence rates when families are large, multigenerational, and reside in stable and relatively isolated communities. In Tasmania for example, two key founder mutations predisposing to Multiple Endocrine Neoplasia Type 1 (MEN 1), have resulted in a prevalence of MEN 1 in Tasmania which is 5-10 fold higher than that reported for other populations (240).

Studies assessing the prevalence of familial forms of PTC indicate that 3.5–6.2% of patients with PTC have one or more first degree relatives with TC (155, 241, 242). An association is known to exist between familial adenomatous polyposis (FAP) and PTC(220, 243, 244). However, a number of reports also describe families in which PTC occurs as a distinct entity, unrelated to FAP(155, 241, 242, 245, 246). The majority of such kindreds contain fewer than four family members affected by PTC.

It is possible that either environmental factors or random association explains the occurrence of PTC in a proportion of these families. However some authors have postulated an autosomal dominant basis for familial PTC (155, 241, 245). Stoffer *et al.* also noted an increased occurrence of nonmalignant thyroid disease in some families with PTC, but the relationship between benign thyroid disease and the subsequent development of malignant papillary lesions was unclear(241). In this chapter, the prevalence and inheritance pattern of PTC in Tasmania is evaluated.

Subjects and Methods

Following approval of the Royal Hobart Hospital Human Research Ethics Committee, all patients identified by the Tasmanian Cancer Registry with a diagnosis of PTC during the period 1978-1998 (n=180, Female:Male=3.5, Age at diagnosis 46.4 ± 1.1) were sought to determine the prevalence of familial PTC. Of these, 99 patients (Female:Male=4.8, Age at diagnosis 44.5 ± 1.0) were living, contactable and consented to provide this information.

Two large Tasmanian kindreds with a family history of PTC were evaluated in detail. Where available, the results of isotope imaging and thyroid histopathology of tissue from fine needle aspiration (FNA) or surgery have been reviewed. A firm diagnosis of PTC could be made in those patients with characteristic histopathology.

Results

In total, 99 PTC patients (male 18, female 81) living, contactable and responded the survey. A family history of TC was reported by 14 (14.1%). Of these, seven respondents belonged to two multigenerational PTC pedigrees that are described in detail below.

Pedigree I

A 62-yr-old female presented with a hoarse voice. A multinodular goiter (MNG) had been noted 2 yr previously. On examination, left vocal cord paralysis and a hard, left sided neck mass were detected. Neck exploration demonstrated locally invasive papillary carcinoma of the thyroid. The patient was treated with total thyroidectomy and 6000 MBq of radio iodine. No evidence of abnormal ¹³¹I uptake was noted on post-ablative whole body scans. Abnormal areas of thallium uptake in the neck and chest were noted, becoming less prominent on consecutive scans. She remains well.

Three of the patient's six children presented with MNG in the ensuing six months (Patients M, N, and P, *Figure 7.1*) and underwent surgical resection. Surgical management was undertaken because of mild compressive symptoms, a low thyrotropin level (indicating unsuitability for thyroxine suppression), or patient anxiety. One patient had FNA of the thyroid preoperatively that was nondiagnostic. PTC was detected during pathological examination in all cases, one microscopic, one 10 mm in diameter, and the other a multifocal PTC. On screening, one of the patient's six children (Patient O) had a solitary nodule confirmed as PTC on excision. Screening other family members yielded two further relatives with MNG who had multifocal PTC (Patients U and W). Patient U

had evidence of malignancy on preoperative FNA. Other relatives with abnormal thyroid glands on screening are shown in *Figure 7.1*.

The family history revealed two additional relatives who had probable thyroid carcinoma (patients B and D). Both had thyroidectomies in their 50's (before 1950) and were reported by relatives and medical practitioners to have thyroid cancer; however, histological confirmation was not possible. There was no family history of colonic malignancy or intestinal polyposis and no history of radiation exposure.

Pedigree II

A 49-yr-old male presented with a 3-week history of left-sided neck swelling. Examination revealed a 1.5 cm mass palpable in the left lobe of the thyroid gland. The patient's family history was unremarkable for thyroid or bowel malignancy, and there was no history of radiation exposure. Following ultrasound and isotope imaging (*Figure 7.1*), the patient underwent hemithyroidectomy, and histopathological examination revealed papillary carcinoma. Total thyroidectomy was subsequently performed, and the patient received a 6000 MBq dose of radio iodine. Follow-up studies to 3 yr have not demonstrated disease recurrence. One year subsequent to presentation of the index case, the patient's monozygotic twin brother presented with a neck mass, assessment of which also revealed PTC, metastatic to a cervical lymph node. In 1995, the 23-yr-old daughter (Patient K) of the index case presented with a right sided thyroid mass, subsequently proven to be an invasive 12 mm PTC. She was treated by total thyroidectomy, ablative radio iodine, and thyroxine suppression. The 22-yr-old daughter of the other twin (Patient L) had a MNG on screening, and a sclerosing papillary microcarcinoma was found on

resection. There has been no evidence of recurrence in any of these family members. The family tree for Pedigree II is also summarized in *Figure 7.1*. The characteristics of surgically treated thyroid disease from both pedigrees are summarized in *Table 7.1*.

Discussion

Familial PTC is relatively uncommon in Tasmania, exhibiting a prevalence (14.1%). Reports by other authors indicate a prevalence in the general population of approximately 5%. The higher prevalence in my study may in part reflect a founder effect associated with pedigree I and II, as well as bias due to a relatively low survey response rate of 55%. However, the kindreds presented herein support the existence of an autosomal dominant inheritance pattern for PTC, separate from the established association with FAP(151). Pedigree I represents one of the largest kindred with non-FAP familial PTC described thus far.

In both families, history and physical examination consistent with FAP or Cowden's syndrome was absent. Although Pedigree II is less extensive, the development of PTC in monozygotic twins (within one year of each other) and in two of their offspring suggests an underlying genetic predisposition to thyroid neoplasia. The fact that both parents and a grandparent of the twins lived to an advanced age without evidence of thyroid cancer suggests the possibility of a *de novo* mutation occurring early in the twin's embryogenesis.

An association may exist between multinodular goitre and PTC. Existing evidence does not exclude this possibility, as thyroid malignancy is thought to be a multi-step process. Furthermore, common genetic factors have been implicated in the pathogenesis of both MNG and PTC (46, 49, 159, 245). It is also possible that the association is indirect, as the presence of MNG is likely to increase the likelihood of diagnosing "occult" PTC(210). However, the clinically significant extent of the majority of tumours

diagnosed in the families described in this study indicates this is not the dominant explanation.

Incomplete penetrance of familial PTC may explain both the obligatory carrier status of patient C in Pedigree I and non-expression of clinically overt thyroid disease. The influence of secondary modifying factors, such as gender may contribute to this, as was the case in pedigree I, where six of seven patients with PTC are female. This observation is similar to that of Lote *et al*, who described a female predilection for PTC in a Norwegian family(245). Both families included individuals with multifocal PTC occurring at a young age, consistent with other reports of familial PTC(159, 247).

The optimal strategy for investigation and management of kindreds with PTC is unclear. Exclusion of undiagnosed FAP would seem prudent, however in the absence of a family history of bowel malignancy, or characteristic physical stigmata of Gardner's syndrome, routine colonic assessment would seem unwarranted. The relatively high risk of PTC developing in an underlying MNG, and the limited value of ultrasonography, isotope scanning, and FNAB in excluding malignancy in the setting of multinodularity, argues strongly for thyroidectomy in family members of high risk pedigrees who have evidence of MNG. The screening strategy currently recommended for these families is periodic thyroid ultrasonography and neck palpation by an experienced examiner(160). Patients with evidence of goiter may then be counseled regarding the potential risk of malignancy and offered the option of early thyroidectomy(160).

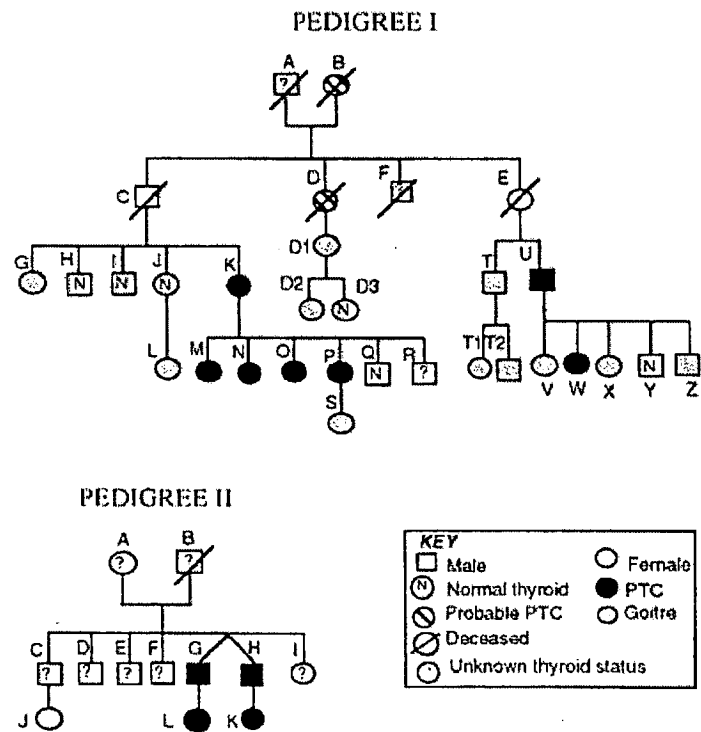
Conclusions

Prior to publication of the paper presented in this chapter, there was limited data available in relation to high penetrance genes associated with autosomal dominant PTC. Careful characterisation of families expressing such patterns of PTC inheritance should result in identification of susceptibility loci for PTC. The large pedigree (Pedigree I) described in this report provided support for the presence of a distinct autosomal dominant form of PTC as well as being the substrate for subsequent genomic localisation studies. Whilst a specific gene is yet to be identified, and familial PTC may arise from a number of distinct genetic loci, the observations reported herein provide impetus for further research.

Table 7.1. Thyroid gland characteristics in patients treated by thyroidectomy

Patient	Age	Ultrasonography; Characteristics on isotope imaging; Thyroid histopathology
(G)	43	Enlarged gland, heterogenous, consistent with MNG; MNG with lymphocytic thyroiditis. No evidence of malignancy
(K)	62	Enlarged nodular gland, consistent with MNG; no dominant nodule; follicular variant of PTC occurring in a MNG
(L)	34	3 x 2.2 cm solitary solid nodule, cold nodule in otherwise normal gland; MNG with benign dominant nodule
(M)	35	Multiple solid and cystic nodules, consistent with MNG; overall uptake increased; dominant nodule with cold areas sclerosing PTC occurring in a MNG
(N)	24	Enlarged gland, 4 nodules; Multifocal PTC
(O)	42	Solid nodule; PTC
(P)	39	Consistent with MNG; overall uptake increased; no dominant cold nodule; sclerosing PTC occurring in a MNG; background of lymphocytic thyroiditis
(T)	58	MNG
(T1)	29	MNG
(T2)	26	2 thyroid nodules, largest 2 cm MNG with lymphocytic thyroiditis
(U)	54	2 thyroid nodules; left lobes; atypical cells on FNA early MNG with multifocal PTC containing follicular variants
(V)	32	2 nodules left lobe early MNG
(W)	23	Multiple nodules, 2–5 mm MNG; multifocal PTC in left lobe
(Z)	27	MNG
I (G)	51	Right lobe enlarged and homogenous, left enlarged; MNG, largest nodule 2 cm large cold area left lobe; generalized patchy uptake well differentiated PTC metastatic to cervical lymph node; solitary follicular adenoma in thyroid gland
I (H)	49	Enlarged gland; nodular left lobe containing a 20 mm solid nodule with patchy tracer uptake consistent with MNG
		PTC containing follicular elements
I (K)	23	Normal sized gland containing 10 mm and 2 mm cold nodules; PTC containing follicular elements
I (L)	22	Lesions in upper left lobe and heterogeneous texture lower pole right lobe normal sized gland, areas of marked decrease in uptake sclerosing papillary microcarcinoma

Figure 7.1 Pedigree charts for family I and II



CHAPTER 8

Conclusion and Future Studies

Thesis Conclusions

This thesis provides the first comprehensive evaluation of TC incidence trends in Australia. Furthermore, the Tasmanian population proved to be a suitable model for evaluating the factors underlying contemporary TC incidence patterns.

A review of notifications to Australian Cancer Registries during the last two decades of the twentieth century demonstrated a progressive rise in the reported incidence of TC. The most pronounced increase occurred during the 1990's and was attributable to an increasing incidence of PTC. The geographic pattern for this trend was most evident in Australia's eastern seaboard States, namely Tasmania, Victoria, New South Wales and Queensland. This distribution co-localised with the ecological pattern of iodine deficiency in Australia. The population of the Australian south-eastern seaboard was mild-moderately iodine deficient prior to introduction of iodine-based disinfectants (iodophors) by the dairy industry in the 1960's. The residual iodine content in milk (related to iodophor use) serendipitously corrected the deficiency. Progressive phase-out of these disinfectants in the late 1980's has been associated with a nationwide decline in iodine nutrition. Over the past decade the population of much of Australia's eastern seaboard has become iodine deficient. Tasmania, recognised as having the lowest pre-iodophor level of iodine nutrition and highest prevalence of endemic goitre, experienced the greatest rise in PTC incidence of all the Australian commonwealth.

However, the information available from the national TC dataset was insufficient to clarify the role of Cancer Registry ascertainment bias, changing trends in medical

practice and altered patterns of PTC risk factor exposure. Addressing these issues required detailed evaluation of a representative population. The Tasmania community was selected for this purpose.

Detailed validation of Tasmanian Cancer Registry case ascertainment was undertaken. This indicated PTC registration was 93.9% complete and without evidence of significant temporal distortion. As this assessment included the period during which PTC incidence doubled, I was able to exclude biased Cancer Registry case ascertainment as an explanation for the observed rise in PTC incidence. This was an important consideration, as prior to this study, time related variation in case ascertainment by cancer registries had been postulated as making an important contribution to observed PTC trends. Furthermore, the morphological classification of tumours over time was found to be stable when independently reviewed. Changes in tumour classification did not account for observed trends in TC incidence.

The dominant change identified by this study was a significant increase in diagnosis of small PTC ($\leq 1\text{cm}$ in maximum dimension). Iodine supplementation of iodine deficient communities has been associated elsewhere with increased diagnosis of PTC of smaller size and earlier stage. Therefore, given the previously identified geographic linkage between increased PTC incidence and the distribution of historical iodine deficiency in Australia, further evaluation of the potential impact changing iodine nutrition on PTC incidence and pathogenesis was undertaken.

Despite two decades of documented iodine sufficiency in Tasmania, PTC incidence increased more than two-fold at the time when iodine deficiency recurred. Whilst not excluding a long latency linking improved iodine nutrition in the 1960's to increased PTC in the 1990's, such a relationship appears unlikely and inconsistent with the expected time course associated with the concept of "papillarisation" following iodine supplementation.

A non-biological association between community iodine supplementation occurring in conjunction with improved community screening for thyroid disease (increasing availability of ultrasonography and consequential interventions such as FNAB and thyroid surgery), appears to be a more plausible link between iodine nutrition and increased incidence of PTC. Similarly, the progressive improvement in medical care and technology occurring in recent decades could similarly increase the diagnosis of "occult" PTC.

A survey and ultrasonographic study was undertaken to determine the prevalence of subclinical and previously diagnosed thyroid disease in Tasmania. The data presented in Chapter 5 indicate a divergence between the absolute risk for nodular thyroid disease (as evidenced by ultrasonography) versus the likelihood of clinically diagnosed and treated thyroid disease. The former was common, irrespective of birth place and residence, whilst the latter was relatively associated with prolonged residence in Tasmania during the era of iodine deficiency. The failure to observe a significant association between place of birth and TC suggests a unique environmental modifier is unlikely to account for PTC incidence trends in Tasmania.

However, the findings were consistent with historically more severe iodine deficiency in Tasmania increasing the prevalence of benign goiter and thyroid dysfunction. Evaluation of these may have secondarily increased the likelihood of diagnosing “occult” PTC. Moreover, thyroid ultrasonography in any person without clinical suspicion of thyroid disease (irrespective of their iodine nutritional history) may also be considered a “risk factor” for FNAB, thyroid surgery and consequently the diagnosis of “occult” PTC.

My results suggested the increase in PTC incidence observed in Tasmania and more widely may in large part be attributable to greater diagnosis of small PTC, many of which are likely to have been asymptomatic, identified by neck ultrasonography and subsequent FNAB. Iodine deficient (or previously deficient) populations can be expected to have a higher prevalence of goitre and larger thyroid nodules. The higher prevalence of clinically apparent structural thyroid disease is likely to increase thyroid imaging, FNAB and consequently the diagnosis of “occult” PTC. Past and present iodine nutrition need have no causal link with PTC pathogenesis, merely serve to modify incidental recognition of existing subclinical nodular thyroid disease.

However, it was also noted that the incidence of PTC larger than 1cm in patients without history of preoperative FNAB had increased in Tasmania, suggesting the occurrence of clinically relevant tumours increased. It was important therefore to examine trends for exposure to established risk factors such as ionising radiation. In the absence of case specific exposure data for fallout to confirm this, Chapter 6 sought to use the *RET/PTC1* rearrangement as a surrogate marker for the involvement of ionising radiation in the

pathogenesis of individual PTC. Observational studies have suggested the *RET/PTC1* rearrangement may occur at higher frequency in PTC arising following thyroidal irradiation.

I was able to map trends for the prevalence of *RET/PTC1* relative to incidence trends for PTC. Whilst the *RET/PTC1* mutation was frequently identified in Tasmanian PTC, there was no clear relationship between *RET/PTC1* and recent PTC incidence trends. This can be interpreted as either a negative finding (in as much as the fraction of PTC with *RET/PTC1* rearrangement failed to increase significantly in parallel with the rise in overall PTC incidence) or conversely, suggestive of a proportional and increasing contribution of ionising radiation to PTC diagnosed in Tasmania. Future research might address this question by undertaking appropriately powered longitudinal studies evaluating populations before and after a documented exposure to fallout.

I also examined the prevalence and genetic basis of familial PTC. A founder effect combined with screening did not account for the rise in PTC incidence observed in Tasmania. The large Tasmanian pedigree described in Chapter 7 provided support for the presence of a distinct autosomal dominant form of PTC as well as a basis for subsequent genomic localisation studies. Whilst a specific gene is yet to be identified, and familial PTC may arise from a number of distinct genetic loci, this manuscript provided impetus for further research.

In summary, this thesis addressed the questions posed in Chapter 1 and reached the following conclusions:

- 1 The incidence of TC increased in Australia during the last two decades of the twentieth century due to a rise in incidence of PTC.
- 2 Geographic variation for PTC incidence in Australia was evident, with the greatest increase occurring in the south-eastern States of Tasmania, Victoria and NSW.
- 3 The Tasmanian population proved to be a suitable model for evaluating the basis for PTC incidence trends given its stable population structure, well documented history of iodine nutrition and stable health care system.
- 4 There was no evidence of any substantial systematic modification to histopathological diagnostic criteria or Cancer Registry case ascertainment and registration protocols to explain observed PTC incidence trends.
- 5 Whilst the incidence of both large and small PTC increased over the study period, greater diagnosis of $PTC \leq 1\text{cm}$ diameter was the dominant factor accounting for the rise in PTC incidence. Increasing use of neck imaging and FNAB in patients with asymptomatic nodular thyroid appear to be the main antecedent factors driving this trend.
- 6 The geographic patterns for PTC incidence trends were compatible with historical and contemporary patterns of iodine deficiency in Australia. The severity of historical deficiency mapped proportionally with the magnitude of recent PTC incidence increases.
- 7 I cannot exclude a direct biological influence of iodine nutrition on PTC pathogenesis, however, the influence of improving and subsequently declining

levels of iodine nutrition in Tasmania over the past four decades appears to have been minimal in comparison to the dominant influence of increasing use of neck ultrasonography and FNAB resulting in diagnosis of “occult” PTC.

- 8 No direct evidence to support ionising radiation in the genesis of contemporary PTC incidence trends has been identified. However, the finding of *RET/PTC1* mutation as highly prevalent in Tasmanian PTC cases warrants further consideration of this possibility.
- 9 Autosomal dominant susceptibility to PTC has been identified in a small proportion of Tasmanian PTC cases, however the impact of familial disease has been relatively minimal on overall PTC incidence trends.
- 10 Based on the data presented in this thesis, it is possible to estimate the relative contributions of ascertainment bias, and changes in underlying biological incidence in contemporary PTC incidence trends. Increased ascertainment of “occult” PTC due to greater use of sensitive neck imaging and contemporary thyroid nodule evaluation paradigms explains the majority of increased PTC diagnoses during the 1990’s, whilst a biologically significant increase in underlying PTC incidence appears responsible for the remainder.

Future Studies

- 1 Follow-up of Tasmanian PTC incidence trends in association with utilization profiles for neck imaging and FNAB to determine if a stable PTC incidence pattern is established consistent with contemporary imaging usage.
- 2 An intervention study based on structured medical practitioner education regarding appropriate use of thyroid ultrasonography to determine if decreased non-specific neck imaging is associated with reduced PTC incidence.
- 3 A large-scale Australian national study, sufficiently powered to assess the impact of changes to national iodine nutrition on PTC incidence.

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